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Molecular actions and clinical pharmacogenetics of lithium therapy

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Abstract

Mood disorders, including bipolar disorder and depression, are relatively common human diseases for which pharmacological treatment options are often not optimal. Among existing pharmacological agents and mood stabilizers used for the treatment of mood disorders, lithium has a unique clinical profile. Lithium has efficacy in the treatment of bipolar disorder generally, and in particular mania, while also being useful in the adjunct treatment of refractory depression. In addition to antimanic and adjunct antidepressant efficacy, lithium is also proven effective in the reduction of suicide and suicidal behaviors. However, only a subset of patients manifests beneficial responses to lithium therapy and the underlying genetic factors of response are not exactly known. Here we discuss preclinical research suggesting mechanisms likely to underlie lithium's therapeutic actions including direct targets inositol monophosphatase and glycogen synthase kinase-3 (GSK-3) among others, as well as indirect actions including modulation of neurotrophic and neurotransmitter systems and circadian function. We follow with a discussion of current knowledge related to the pharmacogenetic underpinnings of effective lithium therapy in patients within this context. Progress in elucidation of genetic factors that may be involved in human response to lithium pharmacology has been slow, and there is still limited conclusive evidence for the role of a particular genetic factor. However, the development of new approaches such as genome-wide association studies (GWAS), and increased use of genetic testing and improved identification of mood disorder patients sub-groups will lead to improved elucidation of relevant genetic factors in the future.

Keywords

Lithium; Bipolar disorder; Depression; Genetics; Candidate gene; Pharmacogenetics

1. Introduction

Mood disorders, bipolar disorder and unipolar depression, are serious diseases with grave consequences for the patient, the patient's family members, and society in terms of the emotional toll, lost productivity, association with other illnesses, and treatment costs. The course of these disorders includes oscillating episodes of mood changes, separated by periods of euthymic normal mood. This unique cyclic nature of bipolar disorder and the multiple disease states makes the negative impact even greater due to the high levels of disease burden and the financial costs associated with the treatment and management (Dilsaver, 2011; Murray et al., 2012).

Multiple treatments for mood disorders are available. Available medications are commonly categorized broadly as mood stabilizers if used primarily for the treatment of bipolar disorder, and labeled as antidepressants when useful for unipolar depression (Hadjipavlou and Yatham, 2008; Schloesser et al., 2012). The definition of "mood stabilizer" is inherently tied to the mood swings that are a primary feature of bipolar disorder, which these medications intend to treat. An ideal mood stabilizer would be effective in preventing occurrences of both manic and depressive episodes of the bipolar disorder over periods of long-term treatment. However, this standard has proven to be too high and the current consensus is that as long as a medication stabilizes some mood related symptoms of bipolar disorder without affecting the others, it can be considered as a mood stabilizer (Baldessarini, 2013). Currently, mood stabilizer medications that are used in the treatment of bipolar disorder include lithium, anticonvulsants (valproate, carbamazepine, and lamotrigine), antipsychotics (e.g., chlorpromazine, olanzapine, quetiapine, risperidone, etc.), and antidepressants (Baldessarini, 2013). While ideally a mood stabilizer should be effective at both poles of bipolar disorder symptoms equally, the current mood stabilizers have an efficacy at one pole but lower efficacy at the other (Rybakowski, 2013). Both unipolar and bipolar depressions are commonly treated with antidepressants belonging to medication classes that act by increasing monoamine activity (serotonin and/or norepinephrine) at the synaptic level. These medications include tricyclics (e.g., desipramine, imipramine), selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, paroxetine, citalopram), and monoamine oxidase inhibitors (MAOIs; e.g., phenelzine, isocarboxazid, tranylcypromine). Refractory depression, and also to a lesser extent mania, may be treated with electroconvulsive therapy (ECT), which was also a primary treatment option for mania prior to the development of pharmacological therapies (Stevens et al., 1996; Loo et al., 2011).

Among these treatment options for mood disorders, lithium is unique. Lithium was the first pharmacological agent that was proven to be effective as a mood stabilizer in the treatment of bipolar disorder (Schou, 2001). Lithium is also a prototypical mood stabilizer as it has robust efficacy in the treatment and prevention of both depressive and manic phases of bipolar disorder, although its antimanic effect is more pronounced than its antidepressant effect (Bauer and Mitchner, 2004; Baldessarini, 2013). Lithium is also unique in the sense

that unlike other medications that are utilized in the treatment of mood disorders, which are originally indicated in the treatment of epilepsy in the case of anticonvulsants or schizophrenia in the case of antipsychotics, lithium is efficacious almost exclusively in the treatment of mood disorders. Indeed, despite the ever-expanding availability of new psychoactive drugs and changing diagnostic criteria of mental diseases, lithium is still recommended as a first-line treatment for bipolar disorder patients (Baldessarini and Tondo 2000; Nivoli, 2011). Lithium therapy's effectiveness in reducing the relapse in bipolar disorder is confirmed by randomized controlled clinical trials (Geddes et al., 2004). Apart from its utility in treatment of bipolar disorder, lithium is also prescribed as an adjunct medication for treatment resistant depression patients in combination with monoamine acting antidepressants (Heninger et al., 1983; Bauer et al., 2003; Bauer et al., 2010). In addition to these therapeutic uses, there is strong evidence indicating the robust efficacy of lithium in reducing the risk of suicide (Kovacsics et al., 2009). Metanalyses indicate superiority of lithium over other treatments in reducing mortality associated with suicide in patients with mood disorders (Cipriani et al., 2005; Baldessarini et al., 2006; Cipriani et al., 2013). However, in addition to a multifaceted and proven efficacy, lithium has a particularly problematic clinical side effect profile. It has a very narrow therapeutic window, which makes overdosing a risk. Even the regular and proper use may lead to severe consequences ranging from weight gain, renal failure, diabetes insipidus, thyroid enlargement (goiter) and hypothyroidism (Schou et al., 1968; Schou, 1984; Adityanjee and Thampy, 2005; Goodwin and Jamison, 2007; Lazarus, 2009; Rej et al., 2012; Werneke et al., 2012). In addition to these side effects, it may take up to two months for lithium to show its full beneficial effects, especially as an antidepressant, and this limits its utility when a fast-acting treatment is needed (Heit and Nemeroff, 1998; Gershon et al., 2009). Therefore, it is important to develop better treatment options, which have the beneficial and unique efficacy of lithium but not the side effects and slow onset of action. To achieve this goal, it is first necessary to understand through which mechanisms and mediating factors, such as genetic background, lithium exerts its therapeutic effects for the treatment of mood disorders.

2. Pharmacogenetic approach to understanding lithium action

While the first discovery of lithium's therapeutic potential to treat bipolar disorder is commonly credited to John Cade, an Australian psychiatrist working at a mental hospital at the end of 1940s, to our knowledge the first record of lithium as an antimanic medication can be dated back to as early as 1871 (discussed by (Mitchell and Hadzi-Pavlovic, 2000)). William Alexander Hammond, a military physician and neurologist who served as Surgeon General for the U.S. Army during the Civil War (Atkinson, 1878) described the use of lithium (as the lithium bromide salt) as a therapy for mania:

“Latterly I have used the bromide of lithium in cases of acute mania and have more reason to be satisfied with it than with any other medicine calculated to diminish the amount of blood in the cerebral vessels, and to calm any nervous excitement that may be present. The rapidity with which its effects are produced renders it specially applicable in such cases. The doses should be large — as high as sixty grains even more — and should be repeated every two or three hours till be produced, or at least till half a dozen doses be taken. After patient has once come

under its influence, the remedy should be continued in smaller doses, taken three or four times in the day.”

[Hammond, 1871, p. 371]

While it could be argued that Hammond might have not realized lithium's therapeutic effect since other bromide salts were used as sedatives at the time (Mitchell and Hadzi-Pavlovic, 2000); Hammond, in addition to his discovery of lithium's effect on acute mania, was remarkably correct in pointing out the specificity of lithium's effect:

“In cases of cerebral congestion attended with illusions and hallucinations but without mania, the other bromides will answer the purpose —preferably the bromide of sodium.”

[Hammond 1871, p. 371]

The cascade of events that led to the broad consideration of lithium's antimanic efficacy in the modern psychiatry era was triggered by John Cade's belief that whatever makes mentally ill patients different than the normal people must have a biochemical basis (Johnson, 1998). His report of lithium efficacy in the medical literature was preceded by a bench to bedside undertaking, which laid the foundation for this discovery. Namely, Cade reported lithium's therapeutic effects in bipolar patients following animal testing that suggested a sedative effect of lithium (Cade, 1949; Johnson, 1998).

Even though the mood stabilizing effect associated with lithium treatment was discovered decades ago, elucidation of its mechanisms of action is still in progress. While lithium itself is one of the simplest elements, understanding how it operates as a psychoactive agent has proven to be far from straightforward. Many putative mechanisms of action have been proposed with no clear conclusion so far (Phiel and Klein, 2001; Gould et al., 2002; Jope, 2003; Gould, 2006; Chiu and Chuang, 2010; Toker et al., 2011). Tremendous insight may lie in the fact that bipolar disorder clearly has a sizable hereditary component. Epidemiological evidence collected from studies on relatives, siblings, and twins of bipolar disorder patients indicates a strong genetic basis of this disease. For instance, while the estimates for prevalence rates of bipolar disorder span from 1% (bipolar type I) to over 4%, depending on whether bipolar disorder type II and subthreshold bipolar disorder are included, monozygotic twins and first-degree relatives of patients are afflicted about 60 and 7% of the time with bipolar disorder, respectively (Craddock and Jones, 1999; Merikangas et al., 2007). More importantly, even though lithium has a unique therapeutic profile in the treatment of bipolar disorder and suicide prevention, only a subset of patients is found to manifest a therapeutic response to lithium. The accumulating evidence indicates that lithium-responsive bipolar disorder patients have a greater likelihood of having relatives with bipolar disorder (Mendlewicz et al., 1973), and a greater chance of having other lithium-responsive relatives (Grof et al., 2002). In contrast, lithium non-responders have a higher frequency of schizophrenia in their family members (Grof et al., 1994). Also, poor responders to lithium are more likely to exhibit an earlier age onset of bipolar disorder symptoms, often in their childhood (Strober et al., 1988). Taken together, manifesting a therapeutic response to lithium among individuals with bipolar disorder appears to be genetically influenced and evidence suggests that lithium-responsive bipolar disorder

patients constitute a distinct subtype (Smeraldi et al., 1984; Smoller, 2003; Alda et al., 2005; Grof, 2010). Therefore, discovering the pharmacogenetics of the lithium therapy response will help in understanding lithium's mechanisms of action and bipolar disorder etiology. In this review, we aim to bring together evidence related to the preclinical and clinical current knowledge of lithium action focusing on the known direct molecular targets of lithium as well as indirect downstream targets — offering our interpretation of the findings from both preclinical and clinical studies. We review human pharmacogenetic studies of lithium, providing discussion of the molecular evidence implicating those genes as potential targets, as well as studies that have looked at the association between these same genes and a mood disorder diagnosis. It is beyond the scope of this present review to discuss all genetic association evidence in mood disorder research. As such, these data are restricted to only those genes where a role (or lack of a role) in lithium response has been reported in the published literature.

3. Lithium and magnesium

Lithium is the lightest metal element and occupies the third location, following hydrogen and helium, in the periodic table. There are no known essential biological functions of lithium in the human body (Aral and Vecchio-Sadus, 2008). As such, it is rather surprising that lithium is also a psychoactive drug with many therapeutic effects for mood disorders. However, the lithium ion, Li^+ , also has the distinction of having an ionic (non-hydrated) radius similar to the ionic radius of magnesium ion, Mg^{2+} , and the ability to compete with magnesium which is a cofactor for some magnesium-dependent enzymes (Mota de Freitas et al., 2006). The widespread functions of magnesium ion as an enzyme cofactor suggest the possibility of widespread effects. However, at therapeutic lithium concentrations (blood levels of lithium found therapeutic in patients; ~0.6 to 1.2 mM) only a modest number of enzymes are documented to be inhibited by lithium at a significant level. Much above this level, e.g., >1.5 mM, lithium itself becomes toxic to the human body (Simard et al., 1989; Wolf and Cittadini, 2003; McKnight et al., 2012). At therapeutic concentrations, lithium is known to inhibit a phosphodiesterase family of enzymes, which includes fructose 1,6-biphosphatase (FBPase), bisphosphate nucleotidase (BPNase), inositol monophosphatase (IMPase), and inositol polyphosphate 1-phosphatase (IPPase) all sharing a common sequence motif (York et al., 1995; Spiegelberg et al., 1999; Gould, 2006). Competition with magnesium for binding sites also modulates actions of lithium on G-protein-mediated cellular signaling transduction pathways (GTP binding and cyclic AMP production) through inhibition of adenylyl cyclase (Ebstein et al., 1976; Ebstein et al., 1978; Andersen and Geisler, 1984; Ebstein et al., 1987; Newman and Belmaker, 1987; Avissar et al., 1988; Mørk and Geisler, 1989; Minadeo et al., 2001; Srinivasan et al., 2004). Lithium selectively inhibits specific isoforms of adenylyl cyclase that are associated with antidepressant-like behaviors in animal models (Mann et al., 2008; Mann et al., 2009).

4. Lithium and the phosphoinositide signaling pathway

Among the above-described family of lithium modulated phosphoesterases, IMPase and IPPase have historically received the most attention due to their relatively early discovery as being inhibited directly by lithium, and involvement in the well characterized

phosphoinositide signaling pathway (Berridge et al., 1989). The phosphoinositide signaling pathway is closely associated with the calcium secondary messenger system and this involvement makes phosphoinositide signaling a critical pathway for many critical cell functions, including but not limited to cell metabolism, fluid secretion and signal processing downstream of neurotransmitter receptors (Berridge, 2009).

The phosphoinositide signaling pathway is activated by G-protein coupled receptors and in certain cases also by tyrosine kinase receptors. Once activated, this pathway leads to the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP₂) via the enzyme phospholipase C (PLC) producing inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol (DAG) (Hilgemann et al., 2001). While IP₃ triggers calcium release into the cytoplasm from the stores of endoplasmic reticulum; DAG activates protein kinase C (PKC) and its downstream targets. Ultimately, IP₃ is used to produce inositol (mostly its stereoisomer, *myo*-inositol), which can be utilized to form the initial step, PIP₂, of the same phosphoinositide signaling pathway (Hilgemann et al., 2001; Gould, 2006). IMPase and IPPase are important enzymes in the process of recycling *myo*-inositol to PIP₂ (Hallcher and Sherman, 1980; Berridge et al., 1989). By preventing such “recycling”, the direct inhibition of IMPase and IPPase by lithium can reduce inositol levels and modulate the phosphoinositide pathway, and by association through this secondary signaling cascade, the actions of a large body of neurotransmitter systems.

The inositol depletion hypothesis, that is, lithium exerts its therapeutic effects by reducing inositol, has been strengthened by a large body of data accumulated over many decades (Manji and Lenox, 1999; Attack, 2000; Williams et al., 2002). Available evidence indicates that lithium reduces inositol levels in the rodent brain, with the most robust results being obtained following acute administration while chronic administration of lithium leads to more modest reductions of brain inositol levels (Allison and Stewart, 1971; Allison et al., 1980; Sherman et al., 1981; Lubrich et al., 1997; Attack, 2000). Moreover, sodium valproate, another mood stabilizer prescribed for bipolar disorder, has been reported to mimic lithium's effects on *myo*-inositol levels (O'Donnell et al., 2000). However, while these preclinical studies generated support for this hypothesis, clinical findings are ambiguous. Moore et al. reported an effect of lithium to decrease brain *myo*-inositol levels in bipolar patient populations, while others have found no effects of lithium on this outcome (Moore et al., 1999; Patel et al., 2006; Forester et al., 2008; Silverstone and McGrath, 2009). Mouse genetic approaches have sometimes, but not always, provided clear evidence for the hypothesis that lithium's therapeutic efficacy is dependent on inositol depletion (Berry et al., 2003; Berry et al., 2004; Cryns et al., 2006; Shaldubina et al., 2006; Cryns et al., 2007; Shaldubina et al., 2007; Bersudsky et al., 2008; Ohnishi et al., 2010).

Human genetic findings that link lithium response to the inositol signaling system are currently limited and not conclusive (Table 1). Similarly, there is non-conclusive evidence linking genetic changes in the inositol signaling system with a mood disorder diagnosis. Polymorphisms in the gene that encodes for one of the two forms of IMPase, *IMP2*, have been associated with the bipolar disorder (Sjoholt et al., 2003; Bloch et al., 2010). However, another, albeit smaller, study did not replicate these results (Dimitrova et al., 2004). Also, a non-association between positive response to lithium and the *IMP2* gene has been reported

(Sjoholt et al., 2003). When it comes to *INPP1*, the gene that encodes for IPPase, the available data are limited and conflicting. A multicenter study found that *INPP1* C973A single nucleotide polymorphism (SNP) was significantly associated with favorable response to lithium therapy among a small number of Norwegian bipolar disorder patients, but this association was not present in an independent Israeli cohort as reported in the same study (Steen et al., 1998). In addition to these data, another study also failed to detect an association between *INPP1* C973A SNP and the lithium therapy response among bipolar disorder patients (Michelon et al., 2006). Furthermore, no link between *INPP1* polymorphisms and a bipolar disorder diagnosis has been observed (Steen et al., 1998; Piccardi et al., 2002). On the other hand, another study found significant associations between polymorphisms in *IMPA2*, *INPP1*, as well as *GSK-3 β* (discussed in more detail in the next section) and higher risk for suicidal behaviors among bipolar disorder patients (Jimenez et al., 2013). A genome-wide significant association between bipolar disorder and three SNPs in the *DGKH* gene that encodes diacylglycerol kinase eta (DGKH) which is an enzyme that metabolizes DAG in the phosphoinositide signaling pathway has been reported (Baum et al., 2008). Later studies added supporting evidence for an association between polymorphisms in the *DGKH* and bipolar disorder (Ollila et al., 2009; Squassina et al., 2009; Takata et al., 2011; Weber et al., 2011; Zeng et al., 2011). However, other studies failed to find such an association (Tesli et al., 2009). Overall these findings tend to indicate that the *DGKH* gene may have a role in the bipolar disorder etiology. However, a lack of an association between three SNPs of the *DGKH* gene and response to lithium treatment in bipolar disorder patients has been reported (Manchia et al., 2009b).

5. Lithium and GSK-3

GSK-3 is an enzyme that was first discovered to deactivate glycogen synthase, the enzyme that converts glucose to glycogen (Embi et al., 1980; Cohen and Frame, 2001; Gould and Manji, 2005). Later, it was discovered that GSK-3 is also inhibited directly by lithium (Klein and Melton, 1996; Stambolic et al., 1996). This direct inhibition is through the competition with magnesium ion (Ryves and Harwood, 2001; Gurvich and Klein, 2002). Indirect inhibition is through increases in inhibitory phosphorylation of GSK-3 β (Chalecka-Franaszek and Chuang, 1999; De Sarno et al., 2002; Zhang et al., 2003). The actions of lithium on GSK-3, as well as the biological effects of this kinase, make this enzyme an important target of mood disorder research.

GSK-3 has two isoforms, α and β , which have 97% sequence homology in their catalytic domains (Frame and Cohen, 2001). Since a high degree of similarity between the functions of these isoforms exists, we refer to them collectively as GSK-3, unless warranted otherwise. GSK-3 is relatively unique among kinases since it is constitutively active in cells, and thus deactivation of GSK-3 is generally responsible for propagation of intracellular signals. The main mechanism of inhibition of GSK-3 is through phosphorylation of its N-terminal serines, 21 and 9 (Cohen and Frame, 2001; Gould, 2006). However, phosphorylation is not the only cellular mechanism used to inhibit GSK-3. In some pathways, binding proteins can also regulate the GSK-3 activity.

GSK-3 is a mediator of the activity of multiple signaling pathways (including AKT, and Wnt signaling), and as such, it has many different roles and effects in various cell functions. This widespread involvement of GSK-3 in the intracellular signaling cascades also extends the list of possible mechanisms by which lithium can exert its effects by the way of inhibiting GSK-3. Akt (also known as protein kinase B) is an intracellular signaling kinase that is activated by the phosphoinositide 3-kinase (PI3K) which itself can be modulated by a variety of signaling pathways including insulin by its tyrosine receptor kinase (Trk) receptors, and brain-derived neurotrophic factor (BDNF) by the TrkB receptors (Fayard et al., 2005; Gould, 2006; Fayard et al., 2011). GSK-3 also functions as a regulator of the Wnt signaling pathway (Gould, 2006). The Wnt pathway is an evolutionarily conserved cellular signaling pathway that is involved in many cell functions including embryonic and tissue development, and cancer (Clevers, 2006). In the Wnt pathway, the main target of GSK-3 is a protein called β -catenin (Gould et al., 2004a). GSK-3 is a part of a destruction complex that phosphorylates β -catenin and this leads to β -catenin's degradation (Clevers and Nusse, 2012; Liu et al., 2012). Activation of the Wnt pathway inhibits GSK-3, blocking degradation of β -catenin and resulting in increased β -catenin-driven gene expression (see (Huang and Klein, 2004; Logan and Nusse, 2004) for review). Through its widespread engagement with different signaling pathways and neuromodulatory systems, GSK-3 is thought to be involved in lithium's therapeutic effects.

There is evidence suggesting that lithium's effect on reducing the hyperlocomotion behavior induced by drugs that increase dopaminergic activity is related to direct actions on GSK-3 (Beaulieu et al., 2004; Prickaerts et al., 2006; Polter et al., 2010; Urs et al., 2012). This hyperlocomotion behavior induced by drugs, such as amphetamine, in rodents is a widely used animal model for the manic phase of bipolar disorder and is especially useful for testing the efficacy of antimanic drugs (Einat et al., 2003b; Gould and Einat, 2007). Clinically, there is evidence that dopamine agonist drugs can increase the susceptibility to mania in bipolar disorder patients and the effects of dopamine agonists, such as methylphenidate, can be lessened with concurrent use of lithium (Mamelak, 1978; Huey et al., 1981; van Kammen et al., 1985; Carlson et al., 1992).

Lithium is also effective in reducing depression-like behaviors in animal models as measured in behavioral tests such as the forced swim test and tail suspension test (O'Brien et al., 2004; Bersudsky et al., 2007; Gould et al., 2008; Can et al., 2011; Can et al., 2013). There is now extensive evidence suggesting that lithium's action to reduce depression-like behaviors seems to be related to effects on GSK-3 (Gould et al., 2004b; Gould et al., 2007; Omata et al., 2011; Zhang et al., 2012).

Due to its close relationship with lithium's mechanisms of action, polymorphisms in GSK-3 genes have received attention (Table 1). One such SNP, -50 T/C (rs334558) is located in the promoter region of *GSK-3 β* gene (Russ et al., 2001). This SNP is functional and the T allele has higher transcriptional activity compared to the C allele (Kwok et al., 2005). Bipolar disorder patient carriers of the rare allele of this SNP have been shown to have a later onset of the disease compared to homozygous carriers of the common allele and homozygous rare allele carrier patients have been shown to manifest a better therapeutic response to total sleep deprivation treatment (Benedetti et al., 2004a, 2004b). Another study that compared

control, bipolar disorder and schizophrenia patients did not detect a significant association between the -50 T/C SNP and these psychiatric conditions (Lee et al., 2006). The difference between carriers of the major and minor allele variants of this SNP also extends to the efficacy of lithium treatment. Homozygous carriers of the common allele (T/T) were reported to have a worse response to lithium treatment compared to carriers of the rare C allele in terms of showing lower recurrence rates of mood swings after the lithium treatment started (Benedetti et al., 2005). Differential response to lithium treatment in the carriers of the rare variant of -50 T/C SNP has been confirmed by an independent study (Adli et al., 2007). However, a study on bipolar disorder patients who had over five years of lithium therapy failed to replicate these results (Szczepankiewicz et al., 2006). Additionally, this same polymorphism is associated with changes in white matter microstructure (specifically axial diffusivity in several white matter fiber tracts, including corpus callosum, forceps major, anterior and posterior cingulum bundle) in lithium-treated patients (Benedetti et al., 2013).

6. Neurotrophic and neuroprotective effects of lithium

Lithium has neuroprotective and neurotrophic effects (Manji et al., 2000; Chiu and Chuang, 2011; Chiu et al., 2013). Chronic lithium exposure prevents glutamate induced excitotoxicity in cultured neurons at human therapeutic doses (Nonaka et al., 1998; Hashimoto et al., 2002). Lithium treatment also attenuates quinolinic acid induced excitotoxicity (Senatorov et al., 2003). Chronic lithium is protective against experimentally induced hypoxia in brain slices and various cerebral ischemia models (Bian et al., 2007; Kim et al., 2008; Omata et al., 2008; Li et al., 2011). Additionally, lithium treatment alone or in combination with valproate is effective in attenuating both physiological and behavioral effects of traumatic brain injury in mouse models (Yu et al., 2012; Yu et al., 2013). In terms of potential mechanisms mediating these actions, lithium treatment has been shown to increase the neuroprotective B cell lymphoma protein-2 (bcl-2) levels in both mouse and rat brains and it can also lead to greater levels of hippocampal neurogenesis and dendritic arborization as well as extracellular signal-regulated kinase (ERK) (Chen et al., 1999; Chen et al., 2000; Einat et al., 2003a, 2003c; Kim et al., 2004; Shim et al., 2013). Interestingly, in the peripheral blood cells of lithium responsive bipolar disorder patients when compared to those who are not responsive increases in the expression levels of pro-survival genes like *BCL2* and decreases in expression of related pro-apoptosis genes have been noted (Lowthert et al., 2012). Chronic lithium exposure increases brain-derived neurotrophic factor (BDNF) in various brain areas including the hippocampus and frontal cortex (Fukumoto et al., 2001; Angelucci et al., 2003; Omata et al., 2008). Mechanistically, lithium may affect BDNF signaling through its inhibition of GSK-3, since BDNF through the TrkB type receptors can lead to modulation of GSK-3. Interestingly the neurotrophic actions of lithium may depend on lithium inhibition of *GSK-3 β* (Chiu and Chuang, 2011). Inhibition of GSK-3 by agents other than lithium also has neurotrophic effects as well (Boku et al., 2008; Dill et al., 2008; Wexler et al., 2008). However, it should be noted that whether lithium's neurotrophic effects are directly mediated through its effect on BDNF signaling is not entirely clear.

Among genetic variations in the *BDNF* gene, the val66met SNP (rs6265) is the most studied. This polymorphism, a result of a single nucleotide substitution, codes for the amino acid methionine in place of valine (Hong et al., 2011). This SNP has important functional consequences. For example, the less common met variant is associated with changes in cognitive performance (Egan et al., 2003; Montag et al., 2010; Soliman et al., 2010). Further, the carriers of rare met allele have lower hippocampal volumes among healthy people and the difference in hippocampal volumes between the carriers of these alleles is even higher among schizophrenia patients (Pezawas et al., 2004; Szeszko et al., 2005; Bueller et al., 2006; Molendijk et al., 2012). The question as to whether this polymorphism is associated with higher risk of bipolar disorder is not satisfactorily answered (Schulze et al., 2003). While some studies indicated that there is an association between increased risk for bipolar disorder and the val66met polymorphism of *BDNF*, others have not confirmed those positive findings (Neves-Pereira et al., 2002; Sklar et al., 2002; Lohoff et al., 2005; Green et al., 2006; Müller et al., 2006; Vincze et al., 2008; Dmitrzak-Węglarz et al., 2010; Sears et al., 2011; Wang et al., 2012). These candidate gene studies, taken together, fail to depict a clear picture on the association between *BDNF* and bipolar disorder susceptibility. A genome-wide association study implicated a SNP in *NTRK2* gene which codes for the TrkB receptor of the *BDNF* signaling cascade as a bipolar disorder risk factor, although this association did not reach genome-wide significance (Smith et al., 2009). In addition to this study, unrelated SNPs in the *NTRK2* gene have been found to be more frequent in bipolar disorder patients compared to controls (Dmitrzak-Węglarz et al., 2010). Two studies, one with Caucasian, and one with Chinese participants found significant associations between lithium treatment response and SNPs in the *NTRK2* gene among bipolar disorder patients (Bremer et al., 2007; Wang et al., 2013). However, another study that investigated the relationship between other polymorphisms of *NTRK2* gene and quality of lithium response in Polish bipolar disorder patients did not find an association (Dmitrzak-Węglarz et al., 2008).

As was the case in the association between the *BDNF* val66met polymorphism and bipolar disorder, the results of studies looking into the association between responding to lithium treatment in bipolar disorder and this polymorphism are conflicting (Table 2). Two related Polish studies found associations between the val66met polymorphism and lithium response showing positive associations between carrying the met allele and a better therapeutic response to lithium (Rybakowski et al., 2005a; Dmitrzak-Węglarz et al., 2008). However, two other studies conducted with different compositions of ethnic groups did not confirm those results (Masui et al., 2006; Michelon et al., 2006).

7. Neurotransmitter systems and lithium

There is evidence that lithium's therapeutic efficacy may involve the serotonergic system due to GSK-3-related mechanisms. Lithium treatment alone can increase 5-HT levels in various brain areas such as dorsal hippocampus and lateral hypothalamus (Baptista et al., 1990; Mørk, 1998). Lithium is also successfully used in refractory depression along with various types of antidepressants (that directly target monoamine systems including 5-HT) as an augmentation therapy (de Montigny et al., 1983; Bauer et al., 2003; Bschor et al., 2003; Bauer et al., 2010). Preclinical studies suggest that this effect of lithium may originate from

the synergy that is created by simultaneous administration of antidepressants and lithium that results in elevated 5-HT transmission levels that are higher than what would be achieved with treatment with antidepressants or lithium alone due to both increased release and reduced reuptake of 5-HT (Okamoto et al., 1996; Muraki et al., 2001; Wegener et al., 2003).

While mechanistically, the serotonergic system is an attractive target for understanding lithium treatment response, studies that investigated the pharmacogenetic associations between the serotonergic system and positive response to lithium treatment have often yielded negative or conflicting results. None of the polymorphisms studied in genes coding for serotonin receptor subtypes 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A} has been shown to be related to the lithium treatment (Serretti et al., 2000; Dmitrzak-Węglarz et al., 2005; Manchia et al., 2009a) (Table 3). It should be noted that these studies excluded assessment of the 5-HT_{1B} receptor subtype which is shown specifically to be relevant to lithium's inhibitory effect on GSK-3 (Polter and Li, 2011). Polymorphisms in the tryptophan hydroxylase (TPH) gene, coding for the rate limiting enzyme in serotonin synthesis, have been implicated in differential response to lithium therapy in a collection of bipolar and major depression patients (Serretti et al., 1999b). However, it is very difficult to relate this finding to a mechanistic understanding of lithium's effects in the brain, since this study was conducted before it was discovered that there are two separate TPH isoforms (TPH-1 and TPH-2), and TPH-2 is mainly responsible for serotonin's neurotransmitter functions in the brain (Walther et al., 2003). Interestingly, a polymorphism in *Tph2* has been associated with both antidepressant responses in depression-like behavior tests. Inbred mice strains that have a lower functioning variant of *Tph2* gene (e.g., BALB/cJ) manifest a reduced response to SSRI treatment as assessed in the forced swim test compared to carriers of the normal functioning variant of *Tph2* (e.g., C57BL/6J) (Cervo et al., 2005; Calcagno et al., 2007; Guzzetti et al., 2008). The same profile of treatment response in different inbred mouse strains was also shown in response to lithium treatment (Can et al., 2011, 2013).

Another potential candidate for genetic basis of response to lithium therapy in the serotonergic system is the serotonin transporter gene (*SLC6A4*). One particular polymorphism in the promoter region of the transporter (5-HTTLPR) changes the serotonin transporter function and leads to long and short variants (Heils et al., 1996). The short variant of the serotonin transporter causes lower serotonin transporter expression and lower reuptake function levels compared to the long variant (Lesch et al., 1996). The short variant of 5-HTTLPR has been implicated in higher risk and severity of mood disorders, vulnerability to stressful life events and altered cortisol response to stress (Collier et al., 1996; Caspi et al., 2003; Kendler et al., 2005; Zalsman et al., 2006; Gotlib et al., 2008; Alexander et al., 2009; Mueller et al., 2011). This polymorphism also interacts with treatment response to antidepressants. Mood disorder patients who are homozygous for the short variant are less responsive to therapy with selective serotonin reuptake inhibitors. However, this effect might be limited to European populations (Smeraldi et al., 1998; Pollock et al., 2000; Zanardi et al., 2000; Yoshida et al., 2002). The evidence for a similar effect on the lithium treatment response is equivocal. Serretti et al. showed that carriers of homozygous short variant of 5-HTTLPR who suffer from mood disorders did not obtain the benefits of lithium treatment at the same level as homozygous or heterozygous long variant

carriers (Serretti et al., 2001). However, this study pooled both bipolar disorder and major depression patients and did not differentiate between manic or depressive episodes. In a follow-up study that had been conducted in a different center, it was found that, contrary to the previous results, bipolar disorder patients who were homozygous carriers of the long variant of 5-HTTLPR were more likely to be non-responders to lithium therapy (Serretti et al., 2004). This result received further support from a study that found that homozygous carriers of the short variant of 5-HTTLPR with treatment resistant depression responded better to lithium augmentation therapy (Stamm et al., 2008). However, another group found a contradictory result indicating that the short variant was associated with a non-response to lithium among bipolar disorder patients (Rybakowski et al., 2005b). While these studies showed some kind of association between 5-HTTLPR variants and lithium response albeit contradictory, two later studies failed to find any significant associations (Michelon et al., 2006; Manchia et al., 2009a; Tharoor et al., 2013).

Contrary to the fact that lithium is intimately involved in dopaminergic signaling through its effects on GSK-3 and Akt, no clear associations between the lithium therapy response and polymorphisms in the components of dopaminergic system have been demonstrated. A polymorphism (rs4532, 48A/G) in the *DRD1* gene that encodes D₁ receptors has been found to be associated with bipolar disorder and the G allele of this polymorphism was implicated as a risk factor for bipolar disorder (Severino et al., 2005; Dmitrzak-Weglarz et al., 2006). A later study, in addition to confirming the finding that the G allele is a risk factor, also showed that this allele is associated with a worse response to lithium treatment in bipolar disorder (Rybakowski et al., 2009). But this finding about lithium therapy response was not replicated by another group of researchers (Manchia et al., 2009a).

While D₂ is closely linked to lithium's GSK-3 mediated effects, D₂ receptor polymorphisms were not associated with bipolar disorder risk along with D₃, D₄ and D₅ receptor polymorphisms and dopamine- β -hydroxylase (Kirov et al., 1999; Leszczynska-Rodziewicz et al., 2005). A series of studies failed to detect an association between polymorphisms in the genes that encode for various dopamine receptors (D₂, D₃, D₄), and enzymes that play a role in dopaminergic metabolism (monoamine oxidase A, catechol-O-methyl transferase) and the response to lithium therapy (Serretti et al., 1998, 1999a; Turecki et al., 1999a; Serretti et al., 2002; Manchia et al., 2009a).

Even though not to the same extent as serotonergic and dopaminergic systems, pharmacogenetics of lithium therapy response in the glutamatergic neurotransmission system have also been studied. Two polymorphisms in the *GRIN2B* gene that encodes one of the subunits of NMDA receptors have been shown to be associated with the risk and symptoms of bipolar disorder (Martucci et al., 2006). However, a study that investigated the *GRIN2B* gene failed to show an association between polymorphisms in this gene and lithium therapy response in bipolar disorder patients (Szczepankiewicz et al., 2009b). *FYN*, a gene that encodes one of the Src family of tyrosine kinases that involve in the regulation of NMDA receptors has also been studied for its possible relationship with the lithium therapy response because it mediates BDNF modulation of certain NMDA receptors (Salter and Kalia, 2004; Xu et al., 2006). However, none of the polymorphisms of the *FYN* gene were statistically significantly associated with favorable lithium therapy response among the

bipolar disorder patients studied, even though a trend was observed toward an association between the T allele of rs3730353 SNP and a worse lithium response (Szczepankiewicz et al., 2009a). A genome-wide association study found suggestive evidence for an association between *GRIA2*, a gene that encodes one of the subunits of AMPA receptors, GluR2, and lithium therapy response in bipolar disorder (Perlis et al., 2009). This finding is further supported by studies indicating that lithium treatment can change the membrane expression of GluR2 in the rodent hippocampus (Du et al., 2008; Gould et al., 2008). However, a later study found no association between *GRIA2* and the bipolar disorder (Chiesa et al., 2012). Interestingly polymorphisms in another gene, *CACNG2* (calcium channel, voltage-dependent, gamma subunit 2, also known as Stargazin) whose protein product is involved in intracellular transportation and regulation of AMPA receptors have been shown to associate with response to lithium therapy (Osten and Stern-Bach, 2006; Silberberg et al., 2008). It is worthwhile to note that a linkage peak of bipolar disorder has been reported near the location of *CACNG2* (Nissen et al., 2012). Another study showed that a functional SNP in the *SLC1A2* gene that encodes one subtype of excitatory amino acid transporters that is responsible for the clearance of extracellular glutamate is associated with the severity of bipolar disorder and interacts with the lithium therapy to mediate response (Haugeto et al., 1996; Dallaspesza et al., 2012). These initial studies are definitely encouraging for further investigation of glutamatergic neurotransmitter system's involvement in lithium therapy response.

Most recently, using a genome-wide association approach, two intronic SNPs in the glutamate decarboxylase-like protein 1 (*GADLI*) gene, were identified to be strongly associated with lithium therapy response ($P = 1.66 \times 10^{-49}$ and $P = 7.07 \times 10^{-50}$) (Chen et al., 2014). This analysis included a discovery cohort of 294 patients, and replication cohorts of 100 and 24 patients. Sequencing identified a 1-base deletion in high linkage disequilibrium with these SNPs, which may have alternative splicing effects on *GADLI* (Chen et al., 2014). It is difficult to predict the possible underlying mechanisms leading to this association since the function of *GADLI* in the nervous system is not currently known (Liu et al., 2012). However, it has sequence similarities with glutamate decarboxylase (GAD) isoforms, the enzyme that catalyzes the glutamate to GABA conversion and is essential for proper functioning of GABAergic synaptic neurotransmission (Liu et al., 2012). While an association between these SNPs and lithium therapy response was identified in three cohorts, it should be kept in mind that this study was conducted in an ethnically homogenous population sample (Han Chinese). Since the SNPs associated with lithium therapy response are only found in Asian populations, it remains to be seen if the results will be extended to other populations (Geer et al., 2010). Additionally, initial attempts to replicate the finding in Asian populations have not supported the published results (T. Schulze, unpublished data). Future studies should also clarify the role of *GADLI* in the nervous system and its precise mechanistic relationship to lithium therapy response.

8. Circadian regulation and lithium

A unique feature of bipolar disorder is the cycling between the manic, euthymic, and depressive phases of the illness and sleep disturbance is a part of bipolar disorder symptomatology (Harvey, 2008). It has been shown that manipulations of circadian clock,

for example with sleep deprivation, has efficacy in the treatment of the depressive phase of bipolar disorder and can increase the likelihood of switching to the hypomanic phase (Colombo et al., 1999; Wu et al., 2009). Administration of lithium can extend the circadian period across a variety of species from *Drosophila*, rodents, non-human primates and humans (McEachron et al., 1981; Johnsson et al., 1983; Possidente and Exner, 1986; Welsh and Moore-Ede, 1990; Hafen and Wollnik, 1994; Dokucu et al., 2005). Mice with a mutation in the *CLOCK* gene whose protein product is an essential part of the circadian system have disruptions of the circadian rhythm and exhibit mania-like behaviors, and these abnormal behaviors can be reversed by chronic lithium treatment (Roybal et al., 2007). Since these findings suggest that the circadian system may play a role in the etiology of bipolar disorder, and in lithium efficacy, a number of pharmacogenetic studies have investigated the role of circadian-related genes in lithium response (Table 4).

Polymorphisms in genes encoding components of the circadian clock system have been associated with the bipolar disorder in various studies. Among these polymorphisms, the 3111 T/C SNP in the *CLOCK* gene has been implicated in the bipolar disorder multiple times, and the C allele was associated with higher rates of recurrence of episodes, reduced sleep and insomnia among bipolar disorder patients (Benedetti et al., 2003; Serretti et al., 2003, 2005). Evening activity levels were observed to be higher in the C allele carriers compared to homozygous T allele carriers, however this difference is only the case in patients who are not undergoing lithium therapy (Benedetti et al., 2007). However, this association between 3111 T/C SNP and the bipolar disorder was not been replicated in an independent study (Nievergelt et al., 2006). In addition to the *CLOCK* gene, polymorphisms in other genes in the circadian clock system, such as *PER3*, *ARNTL*, *TIMELESS*, *ARNTL2*, *DBP*, *VIP*, and *NR1D1* have been associated with the bipolar disorder (Mansour et al., 2006; Nievergelt et al., 2006; Benedetti et al., 2008; Shi et al., 2008; Soria et al., 2010) (for a review see (Dallaspezia and Benedetti, 2009)). However, polymorphisms in *ARNTL*, *CLOCK*, *PER2*, *PER3* were not shown be associated with the lithium therapy response (McCarthy et al., 2011) (Table 4). Of particular interest, the protein product of *NR1D1* gene, Rev-Erba is a promising target for understanding lithium's therapeutic efficacy in bipolar disorder. Knockout mice that are missing Rev-erba manifest shorter circadian period (Preitner et al., 2002). Rev-erba is also a phosphorylation target of GSK-3 and without this phosphorylation the Rev-erba protein degrades and this effect can be achieved with lithium's inhibition of GSK-3 (Yin et al., 2006). Therefore, it is plausible that lithium's effect on circadian period length and possibly on the bipolar disorder involves this mechanism. Recent studies showed that two SNPs in the *NR1D1* gene have been nominally associated with a favorable treatment response to lithium therapy among bipolar disorder patients, while multiple other SNPs in this gene were not associated at all (Manchia et al., 2009b; Campos-de-Sousa et al., 2010; McCarthy et al., 2011). However, these studies did not directly confirm each other's findings, because the associations were identified between different SNPs in the *NR1D1* gene and lithium therapy response (Campos-de-Sousa et al., 2010; McCarthy et al., 2011). While it is not clear how the polymorphisms in *NR1D1* gene may affect the GSK-3 and Rev-erba interaction, this finding deserves further study.

9. Conclusions and future directions

To date, in search of the genetic basis of differential response to lithium therapy, much of the research effort has been devoted to candidate genes that have been identified to be possibly related to lithium's mechanisms of action in preclinical studies. While a small number of genome-wide association and linkage studies have been conducted, these studies generally only arrived at suggestive results or, by design, could not pinpoint the exact genes involved (Turecki et al., 1999b, 2001; Schulze, 2010); for a review see (Cruceanu et al., 2011). The most recent significant genome-wide association finding implicating the *GADL1* gene requires additional replication and the mechanistic implications are not known (Chen et al., 2014). Candidate-gene studies thus constitute a bulk of the available positive data supporting individual genes and lithium response. However, these studies usually are based on small sample sizes, limited geographical reach, and at times differences in terms of diagnosis and treatment of bipolar disorder that may explain frequent contradictory results coming from different research groups. Another issue in most studies is the skewed gender distribution biased toward females among study participants. This may be due to greater availability of female participants. Overall, the majority of research efforts have been concentrated on a select group of direct targets of lithium, while leaving the others unstudied such as FBPase (fructose-1,6-bisphosphatase), BPNase (bisphosphate nucleotidase) and PGM (phosphoglucomutase) (Gould et al., 2004c). Most of the studies reviewed here involve retrospective study design, which limits the reliability of lithium response assessments of patients since retrospective studies, at least partly, have to rely on self-reports and recall of life events by the patients. The lack of uniformity in lithium treatment regimens among patients is also a limiting factor for this type of study. From a purely scientific standpoint, randomized placebo controlled prospective study designs are preferable over retrospective designs. However, because of ethical concerns regarding assigning patients to a placebo group especially when the risk of suicide is present, such prospective studies are extremely difficult to conduct with adequate sample sizes. Another issue that makes making progress in unraveling the pharmacogenetics of lithium treatment challenging is the lack of homogeneity between studies in terms of the definition and degrees of lithium treatment responses in the literature. This issue can be addressed by utilization of a uniform definition of lithium treatment (Grof et al., 2002). The heterogeneity in the definitions of lithium treatment response has been further exacerbated by the lack of consensus between separate studies involving parameters such as length of lithium treatment, the degree of symptom reduction, inclusion and exclusion criteria of patients with comorbid conditions, and whether other psychoactive medications were administered. Finally, in many cases the functional consequences of polymorphisms in genes that are associated with bipolar disorder or treatment are not known. This makes it difficult for many findings that do exist to contribute a meaningful mechanistic understanding of lithium therapy response.

Some of these issues will be addressed by the work of the Consortium of Lithium Genetics (www.ConLiGen.org; (Schulze et al., 2010)), an international collaborative effort established in 2008. To date, ConLiGen has brought together leading groups from Europe, the Americas, Asia, and Australia to create the largest resource for pharmacogenetic studies in lithium-treated bipolar patients. Using a stringent and standardized definition of lithium

response across all sites, ConLiGen will soon have completed a GWAS of lithium response in close to 3000 samples (Schulze et al., 2010). ConLiGen applies a previously developed and subsequently widely used treatment response scale (Grof et al., 2002). This scale was specifically designed to retrospectively assess lithium response, based on medical records, an interview with the patient, or a combination thereof. For the use of this scale in their multinational genetic studies, comprising centers with different traditions and experiences with the use of lithium, the ConLiGen network performed a systematic training of raters, followed by a thorough assessment of interrater reliability across all sites. Moderate to substantial agreement was shown, with kappa values reaching 0.66 for a dichotomous response definition, and intraclass correlation of 0.75 for a continuous definition of response (Manchia et al., 2013). Beyond the study of lithium response, the ConLiGen data and biomaterial repository will serve as a unique resource for a variety of pharmacogenetic studies in bipolar disorder, including investigations on adverse events or other pharmacological agents.

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References

- Adityanjee M, Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol.* 2005; 28:38–49. [PubMed: 15714160]
- Adli M, Hollinde DL, Stamm T, Wiethoff K, Tsafrir M, Kirchheiner J, et al. Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta -50T/C single nucleotide polymorphism. *Biol Psychiatry.* 2007; 62:1295–302. [PubMed: 17628506]
- Alda M, Grof P, Rouleau GA, Turecki G, Young LT. Investigating responders to lithium prophylaxis as a strategy for mapping susceptibility genes for bipolar disorder. *Prog Neuro-Psychopharmacol Biol Psychiatry.* 2005; 29:1038–45.
- Alexander N, Kuepper Y, Schmitz A, Osinsky R, Kozyra E, Hennig J. Gene–environment interactions predict cortisol responses after acute stress: implications for the etiology of depression. *Psychoneuroendocrinology.* 2009; 34:1294–303. [PubMed: 19410377]
- Allison JH, Boshans RL, Hallcher LM, Packman PM, Sherman WR. The effects of lithium on *myo*-inositol levels in layers of frontal cerebral cortex, in cerebellum, and in corpus callosum of the rat. *J Neurochem.* 1980; 34:456–8. [PubMed: 7411156]
- Allison JH, Stewart MA. Reduced brain inositol in lithium-treated rats. *Nat New Biol.* 1971; 233:267–8. [PubMed: 5288124]
- Andersen PH, Geisler A. Lithium inhibition of forskolin-stimulated adenylate cyclase. *Neuropsychobiology.* 1984; 12:1–3. [PubMed: 6542629]
- Angelucci F, Aloe L, Jimenez-Vasquez P, Mathe AA. Lithium treatment alters brain concentrations of nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor in a rat model of depression. *Int J Neuropsychopharmacol.* 2003; 6:225–31. [PubMed: 12974988]
- Aral H, Vecchio-Sadus A. Toxicity of lithium to humans and the environment — a literature review. *Ecotoxicol Environ Saf.* 2008; 70:349–56. [PubMed: 18456327]
- Atack, JR. Lithium, phosphatidylinositol signaling, and bipolar disorder. In: Manji, HK.; Bowden, CL.; Belmaker, RH., editors. *Bipolar medications: mechanism of action.* Washington, DC: American Psychiatric Press, Inc; 2000.
- Atkinson, WB. *The physicians and surgeons of the United States.* Charles Robson; Philadelphia: 1878.

- Avissar S, Schreiber G, Danon A, Belmaker RH. Lithium inhibits adrenergic and cholinergic increases in GTP binding in rat cortex. *Nature*. 1988; 331:440–2. [PubMed: 3340189]
- Baldessarini, R. *Chemotherapy in psychiatry*. Springer; New York: 2013. Mood-stabilizing agents; p. 89-154.
- Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord*. 2006; 8:625–39. [PubMed: 17042835]
- Baptista T, Hernandez L, Burguera J, Burguera M, Hoebel B. Chronic lithium administration enhances serotonin release in the lateral hypothalamus but not in the hippocampus in rats. A microdialysis study. *J Neural Transm*. 1990; 82:31–41.
- Bauer M, Adli M, Bschor T, Pilhatsch M, Pfennig A, Sasse J, et al. Lithium's emerging role in the treatment of refractory major depressive episodes: augmentation of antidepressants. *Neuropsychobiology*. 2010; 62:36–42. [PubMed: 20453533]
- Bauer M, Forsthoff A, Baethge C, Adli M, Berghofer A, Dopfner S, et al. Lithium augmentation therapy in refractory depression — update 2002. *Eur Arch Psychiatry Clin Neurosci*. 2003; 253:132–9. [PubMed: 12904977]
- Bauer MS, Mitchner L. What is a “mood stabilizer”? An evidence-based response. *Am J Psychiatry*. 2004; 161:3–18. [PubMed: 14702242]
- Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, et al. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Mol Psychiatry*. 2008; 13:197–207. [PubMed: 17486107]
- Beaulieu JM, Sotnikova TD, Yao WD, Kockeritz L, Woodgett JR, Gainetdinov RR, et al. Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. *Proc Natl Acad Sci U S A*. 2004; 101:5099–104. [PubMed: 15044694]
- Benedetti F, Bernasconi A, Lorenzi C, Pontiggia A, Serretti A, Colombo C, et al. A single nucleotide polymorphism in glycogen synthase kinase 3- β promoter gene influences onset of illness in patients affected by bipolar disorder. *Neurosci Lett*. 2004a; 355:37–40. [PubMed: 14729229]
- Benedetti F, Bollettini I, Barberi I, Radaelli D, Poletti S, Locatelli C, et al. Lithium and GSK3- β promoter gene variants influence white matter microstructure in bipolar disorder. *Neuropsychopharmacology*. 2013; 38:313–27. [PubMed: 22990942]
- Benedetti F, Dallaspezia S, Colombo C, Pirovano A, Marino E, Smeraldi E. A length polymorphism in the circadian *CLOCK* gene Per3 influences age at onset of bipolar disorder. *Neurosci Lett*. 2008; 445:184–7. [PubMed: 18789374]
- Benedetti F, Dallaspezia S, Fulgosi MC, Lorenzi C, Serretti A, Barbini B, et al. Actimetric evidence that *CLOCK* 3111T/C SNP influences sleep and activity patterns in patients affected by bipolar depression. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B:631–5. [PubMed: 17221848]
- Benedetti F, Serretti A, Colombo C, Barbini B, Lorenzi C, Campori E, et al. Influence of *CLOCK* gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet B Neuropsychiatr Genet*. 2003; 123:23–6. [PubMed: 14582141]
- Benedetti F, Serretti A, Colombo C, Lorenzi C, Tubazio V, Smeraldi E. A glycogen synthase kinase 3- β promoter gene single nucleotide polymorphism is associated with age at onset and response to total sleep deprivation in bipolar depression. *Neurosci Lett*. 2004b; 368:123–6. [PubMed: 15351432]
- Benedetti F, Serretti A, Pontiggia A, Bernasconi A, Lorenzi C, Colombo C, et al. Long-term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3- β -50T/C SNP. *Neurosci Lett*. 2005; 376:51–5. [PubMed: 15694273]
- Berridge MJ. Inositol trisphosphate and calcium signalling mechanisms. *Biochim Biophys Acta, Mol Cell Res*. 2009; 1793:933–40.
- Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. *Cell*. 1989; 59:411–9. [PubMed: 2553271]
- Berry GT, Buccafusca R, Greer JJ, Eccleston E. Phosphoinositide deficiency due to inositol depletion is not a mechanism of lithium action in brain. *Mol Genet Metab*. 2004; 82:87–92. [PubMed: 15110328]

- Berry GT, Wu S, Buccafusca R, Ren J, Gonzales LW, Ballard PL, et al. Loss of murine Na⁺/*myo*-inositol cotransporter leads to brain *myo*-inositol depletion and central apnea. *J Biol Chem*. 2003; 278:18297–302. [PubMed: 12582158]
- Bersudsky Y, Shaldubina A, Agam G, Berry GT, Belmaker RH. Homozygote inositol transporter knockout mice show a lithium-like phenotype. *Bipolar Disord*. 2008; 10:453–9. [PubMed: 18452441]
- Bersudsky Y, Shaldubina A, Belmaker RH. Lithium's effect in forced-swim test is blood level dependent but not dependent on weight loss. *Behav Pharmacol*. 2007; 18:77–80. [PubMed: 17218800]
- Bian Q, Shi T, Chuang D-M, Qian Y. Lithium reduces ischemia-induced hippocampal CA1 damage and behavioral deficits in gerbils. *Brain Res*. 2007; 1184:270–6. [PubMed: 18028886]
- Bloch PJ, Weller AE, Doyle GA, Ferraro TN, Berrettini WH, Hodge R, et al. Association analysis between polymorphisms in the *myo*-inositol monophosphatase 2 (IMPA2) gene and bipolar disorder. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2010; 34:1515–9.
- Boku S, Nakagawa S, Masuda T, Nishikawa H, Kato A, Kitaichi Y, et al. Glucocorticoids and lithium reciprocally regulate the proliferation of adult dentate gyrus-derived neural precursor cells through GSK-3[β] and [β]-catenin/TCF pathway. *Neuropsychopharmacology*. 2008; 34:805–15. [PubMed: 19005466]
- Bremer T, Diamond C, McKinney R, Shehktman T, Barrett TB, Herold C, et al. The pharmacogenetics of lithium response depends upon clinical co-morbidity. *Mol Diagn Ther*. 2007; 11:161–70. [PubMed: 17570738]
- Bschor T, Lewitzka U, Sasse J, Adli M, Köberle U, Bauer M. Lithium augmentation in treatment-resistant depression: clinical evidence, serotonergic and endocrine mechanisms. *Pharmacopsychiatry*. 2003; 36:S230. [PubMed: 14677084]
- Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubieta J-K. BDNF val66met allele is associated with reduced hippocampal volume in healthy subjects. *Biol Psychiatry*. 2006; 59:812–5. [PubMed: 16442082]
- Cade JF. Lithium salts in the treatment of psychotic excitement. *Medical Journal of Australia*. 1949
- Calcagno E, Canetta A, Guzzetti S, Cervo L, Invernizzi RW. Strain differences in basal and post-citalopram extracellular 5-HT in the mouse medial prefrontal cortex and dorsal hippocampus: relation with tryptophan hydroxylase-2 activity. *J Neurochem*. 2007; 103:1111–20. [PubMed: 17666043]
- Campos-de-Sousa S, Guindalini C, Tondo L, Munro J, Osborne S, Floris G, et al. Nuclear receptor Rev-Erb- α circadian gene variants and lithium carbonate prophylaxis in bipolar affective disorder. *J Biol Rhythm*. 2010; 25:132–7.
- Can A, Blackwell RA, Piantadosi SC, Dao DT, O'Donnell KC, Gould TD. Antidepressant-like responses to lithium in genetically diverse mouse strains. *Genes Brain Behav*. 2011; 10:434–43. [PubMed: 21306560]
- Can A, Piantadosi S, Gould T. Differential antidepressant-like response to lithium treatment between mouse strains: effects of sex, maternal care, and mixed genetic background. *Psychopharmacology*. 2013:1–8.
- Carlson GA, Rapport MD, Kelly KL, Pataki CS. The effects of methylphenidate and lithium on attention and activity level. *J Am Acad Child Adolesc Psychiatry*. 1992; 31:262–70. [PubMed: 1564028]
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Sci Signal*. 2003; 301:386.
- Cervo L, Canetta A, Calcagno E, Burbassi S, Sacchetti G, Caccia S, et al. Genotype-dependent activity of tryptophan hydroxylase-2 determines the response to citalopram in a mouse model of depression. *J Neurosci*. 2005; 25:8165–72. [PubMed: 16148224]
- Chalecka-Franaszek E, Chuang DM. Lithium activates the serine/threonine kinase Akt-1 and suppresses glutamate-induced inhibition of Akt-1 activity in neurons. *Proc Natl Acad Sci U S A*. 1999; 96:8745–50. [PubMed: 10411946]

- Chen C-H, Lee C-S, Lee M-TM, Ouyang W-C, Chen C-C, Chong M-Y, et al. Variant GADL1 and response to lithium therapy in bipolar I disorder. *N Engl J Med*. 2014; 370:119–28. [PubMed: 24369049]
- Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. *J Neurochem*. 2000; 75:1729–34. [PubMed: 10987856]
- Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH, et al. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. *J Neurochem*. 1999; 72:879–82. [PubMed: 9930766]
- Chiesa A, Crisafulli C, Porcelli S, Balzarro B, Han C, Patkar AA, et al. Case–control association study of GRIA1, GRIA2 and GRIA4 polymorphisms in bipolar disorder. *Int J Psychiatry Clin Pract*. 2012; 16:18–26. [PubMed: 22122651]
- Chiu C-T, Chuang D-M. Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders. *Pharmacol Ther*. 2010; 128:281–304. [PubMed: 20705090]
- Chiu C-T, Chuang D-M. Neuroprotective action of lithium in disorders of the central nervous system. *Zhong nan da xue xue bao Yi xue banJ Cent South Univ Med Sci*. 2011; 36:461.
- Chiu C-T, Wang Z, Hunsberger JG, Chuang D-M. Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. *Pharmacol Rev*. 2013; 65:105–42. [PubMed: 23300133]
- Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ*. 2013:346.
- Cipriani A, Pretty H, Hawton K, Geddes JR. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. *Am J Psychiatry*. 2005; 162:1805–19. [PubMed: 16199826]
- Clevers H. Wnt/ β -catenin signaling in development and disease. *Cell*. 2006; 127:469–80. [PubMed: 17081971]
- Clevers H, Nusse R. Wnt/ β -catenin signaling and disease. *Cell*. 2012; 149:1192–205. [PubMed: 22682243]
- Cohen P, Frame S. The renaissance of GSK3. *Nat Rev Mol Cell Biol*. 2001; 2:769–76. [PubMed: 11584304]
- Collier D, Stöber G, Li T, Heils A, Catalano M, Di Bella D, et al. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol Psychiatry*. 1996; 1:453. [PubMed: 9154246]
- Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Res*. 1999; 86:267–70. [PubMed: 10482346]
- Craddock N, Jones I. Genetics of bipolar disorder. *J Med Genet*. 1999; 36:585–94. [PubMed: 10465107]
- Cruceanu C, Alda M, Rouleau G, Turecki G. Response to treatment in bipolar disorder. *Curr Opin Psychiatry*. 2011; 24:24. [PubMed: 21088584]
- Cryns K, Shamir A, Shapiro J, Daneels G, Goris I, Van Craenendonck H, et al. Lack of lithium-like behavioral and molecular effects in IMPA2 knockout mice. *Neuropsychopharmacology*. 2006; 32(4):881–91. [PubMed: 16841073]
- Cryns K, Shamir A, Van Acker N, Levi I, Daneels G, Goris I, et al. IMPA1 is essential for embryonic development and lithium-like pilocarpine sensitivity. *Neuropsychopharmacology*. 2007; 33:674–84. [PubMed: 17460611]
- Dallaspezia S, Benedetti F. Melatonin, circadian rhythms, and the *CLOCK* genes in bipolar disorder. *Curr Psychiatry Rep*. 2009; 11:488–93. [PubMed: 19909672]
- Dallaspezia S, Poletti S, Lorenzi C, Pirovano A, Colombo C, Benedetti F. Influence of an interaction between lithium salts and a functional polymorphism in SLC1A2 on the history of illness in bipolar disorder. *Mol Diagn Ther*. 2012; 16:303–9. [PubMed: 23023733]
- de Montigny C, Cournoyer G, Morissette R, Langlois R, Caille G. Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression. Correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system. *Arch Gen Psychiatry*. 1983; 40:1327–34. [PubMed: 6418109]

- De Sarno P, Li X, Jope RS. Regulation of Akt and glycogen synthase kinase-3 β phosphorylation by sodium valproate and lithium. *Neuropharmacology*. 2002; 43:1158–64. [PubMed: 12504922]
- Dill J, Wang H, Zhou F, Li S. Inactivation of glycogen synthase kinase 3 promotes axonal growth and recovery in the CNS. *J Neurosci*. 2008; 28:8914–28. [PubMed: 18768685]
- Dilsaver SC. An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. *J Affect Disord*. 2011; 129:79–83. [PubMed: 20888048]
- Dimitrova A, Milanova V, Krastev S, Nikolov I, Toncheva D, Owen MJ, et al. Association study of *myo*-inositol monophosphatase 2 (IMPA2) polymorphisms with bipolar affective disorder and response to lithium treatment. *Pharmacogenomics J*. 2004; 5:35–41. [PubMed: 15505643]
- Dmitrzak-Węglarz M, Rybakowski JK, Slopian A, Czerski PM, Leszczynska-Rodziewicz A, Kapelski P, et al. Dopamine receptor D₁ gene –48A/G polymorphism is associated with bipolar illness but not with schizophrenia in a Polish population. *Neuropsychobiology*. 2006; 53:46–50. [PubMed: 16397404]
- Dmitrzak-Węglarz M, Rybakowski JK, Suwalska A, Skibinska M, Leszczynska-Rodziewicz A, Szczepankiewicz A, et al. Association studies of the BDNF and the NTRK2 gene polymorphisms with prophylactic lithium response in bipolar patients. *Pharmacogenomics*. 2008; 9:1595–603. [PubMed: 19018715]
- Dmitrzak-Węglarz M, Rybakowski JK, Suwalska A, Slopian A, Czerski PM, Leszczynska-Rodziewicz A, et al. Association studies of 5-HT_{2A} and 5-HT_{2C} serotonin receptor gene polymorphisms with prophylactic lithium response in bipolar patients. *Pharmacol Rep*. 2005; 57:761–5. [PubMed: 16382194]
- Dmitrzak-Węglarz M, Skibińska M, Szczepankiewicz A, Leszczynska-Rodziewicz A, Kapelski P, Czerski P, et al. Association analysis of polymorphisms of the NTRK2 and BDNF genes with bipolar affective disorder in a Polish sample. *Arch Psychiatry Psychother*. 2010; 2:5–16.
- Dokucu ME, Yu L, Taghert PH. Lithium- and valproate-induced alterations in circadian locomotor behavior in *Drosophila*. *Neuropsychopharmacology*. 2005; 30:2216–24. [PubMed: 15956996]
- Du J, Creson TK, Wu L-J, Ren M, Gray NA, Falke C, et al. The role of hippocampal GluR1 and GluR2 receptors in manic-like behavior. *J Neurosci*. 2008; 28:68–79. [PubMed: 18171924]
- Ebstein R, Belmaker R, Grunhaus L, Rimón R. Lithium inhibition of adrenaline-stimulated adenylate cyclase in humans. *Nature*. 1976; 259:411–3. [PubMed: 175287]
- Ebstein RP, Moscovitch D, Zeevi S, Amiri Z, Lerer B. Effect of lithium in vitro and after chronic treatment on human platelet adenylate cyclase activity: postreceptor modification of second messenger signal amplification. *Psychiatry Res*. 1987; 21:221–8. [PubMed: 2819913]
- Ebstein RP, Reches A, Belmaker RH. Lithium inhibition of the adenosine-induced increase of adenylate cyclase activity. *J Pharm Pharmacol*. 1978; 30:122–3. [PubMed: 24099]
- Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003; 112:257–69. [PubMed: 12553913]
- Einat H, Manji H, Gould T, Du J, Chen G. Possible involvement of the ERK signaling cascade in bipolar disorder: behavioral leads from the study of mutant mice. *Drug News Perspect*. 2003a; 16:453–63. [PubMed: 14668941]
- Einat H, Manji HK, Belmaker RH. New approaches to modeling bipolar disorder. *Psychopharmacol Bull*. 2003b; 37:47–63. [PubMed: 14561948]
- Einat H, Yuan P, Gould TD, Li J, Du J, Zhang L, et al. The role of the extracellular signal-regulated kinase signaling pathway in mood modulation. *J Neurosci*. 2003c; 23:7311–6. [PubMed: 12917364]
- Embi N, Rylatt DB, Cohen P. Glycogen synthase kinase-3 from rabbit skeletal muscle Separation from cyclic-AMP-dependent protein kinase and phosphorylase kinase. *Eur J Biochem*. 1980; 107:519–27. [PubMed: 6249596]
- Fayard E, Tintignac LA, Baudry A, Hemmings BA. Protein kinase B/Akt at a glance. *J Cell Sci*. 2005; 118:5675–8. [PubMed: 16339964]
- Fayard, E.; Xue, G.; Parcellier, A.; Bozulic, L.; Hemmings, B. Protein kinase B (PKB/Akt), a key mediator of the PI3K signaling pathway. In: Rommel, C.; Vanhaesebroeck, B.; Vogt, PK., editors. *Phosphoinositide 3-kinase in health and disease*. Berlin Heidelberg: Springer; 2011. p. 31-56.

- Forester BP, Finn CT, Berlow YA, Wardrop M, Renshaw PF, Moore CM. Brain lithium, N-acetyl aspartate and *myo*-inositol levels in older adults with bipolar disorder treated with lithium: a lithium-7 and proton magnetic resonance spectroscopy study. *Bipolar Disord*. 2008; 10:691–700. [PubMed: 18837863]
- Frame S, Cohen P. GSK3 takes centre stage more than 20 years after its discovery. *Biochem J*. 2001; 359:1–16. [PubMed: 11563964]
- Fukumoto T, Morinobu S, Okamoto Y, Kagaya A, Yamawaki S. Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. *Psychopharmacology (Berl)*. 2001; 158:100–6. [PubMed: 11685390]
- Geer LY, Marchler-Bauer A, Geer RC, Han L, He J, He S, et al. The NCBI BioSystems database. *Nucleic Acids Res*. 2010; 38:D492–6. [PubMed: 19854944]
- Gershon S, Chengappa KNR, Malhi GS. Lithium specificity in bipolar illness: a classic agent for the classic disorder. *Bipolar Disord*. 2009; 11:34–44. [PubMed: 19538684]
- Goodwin, FK.; Jamison, KR. Manic-depressive illness. 2. Oxford University Press New York; Oxford: 2007.
- Gotlib IH, Joormann J, Minor KL, Hallmayer J. HPA-axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biol Psychiatry*. 2008; 63:847. [PubMed: 18005940]
- Gould TD. Targeting glycogen synthase kinase-3 as an approach to develop novel mood-stabilising medications. *Expert Opin Ther Targets*. 2006; 10:377–92. [PubMed: 16706678]
- Gould TD, Chen G, Manji HK. Mood stabilizer psychopharmacology. *Clin Neurosci Res*. 2002; 2:193–212. [PubMed: 22707923]
- Gould TD, Chen G, Manji HK. In vivo evidence in the brain for lithium inhibition of glycogen synthase kinase-3. *Neuropsychopharmacology*. 2004a; 29:32–8. [PubMed: 12942141]
- Gould TD, Einat H. Animal models of bipolar disorder and mood stabilizer efficacy: a critical need for improvement. *Neurosci Biobehav Rev*. 2007; 31:825–31. [PubMed: 17628675]
- Gould TD, Einat H, Bhat R, Manji HK. AR-A014418, a selective GSK-3 inhibitor, produces antidepressant-like effects in the forced swim test. *Int J Neuropsychopharmacol*. 2004b; 7:387–90. [PubMed: 15315719]
- Gould TD, Einat H, O'Donnell KC, Picchini AM, Schloesser RJ, Manji HK. Beta-catenin overexpression in the mouse brain phenocopies lithium-sensitive behaviors. *Neuropsychopharmacology*. 2007; 32:2173–83. [PubMed: 17299510]
- Gould TD, Manji HK. Glycogen synthase kinase-3: a putative molecular target for lithium mimetic drugs. *Neuropsychopharmacology*. 2005; 30:1223–37. [PubMed: 15827567]
- Gould TD, O'Donnell KC, Dow ER, Du J, Chen G, Manji HK. Involvement of AMPA receptors in the antidepressant-like effects of lithium in the mouse tail suspension test and forced swim test. *Neuropharmacology*. 2008; 54:577–87. [PubMed: 18096191]
- Gould TD, Quiroz JA, Singh J, Zarate CA, Manji HK. Emerging experimental therapeutics for bipolar disorder: insights from the molecular and cellular actions of current mood stabilizers. *Mol Psychiatry*. 2004c; 9:734–55. [PubMed: 15136794]
- Green EK, Raybould R, Macgregor S, Hyde S, Young AH, O'Donovan MC, et al. Genetic variation of brain-derived neurotrophic factor (BDNF) in bipolar disorder: case-control study of over 3000 individuals from the UK. *Br J Psychiatry*. 2006; 188:21–5. [PubMed: 16388065]
- Grof P. Sixty years of lithium responders. *Neuropsychobiology*. 2010; 62:8–16. [PubMed: 20453530]
- Grof P, Alda M, Gror E, Zvolsky P, Walsh M. Lithium response and genetics of affective disorders. *J Affect Disord*. 1994; 32:85–95. [PubMed: 7829768]
- Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, et al. Is response to prophylactic lithium a familial trait? *J Clin Psychiatry*. 2002; 63:942–7. [PubMed: 12416605]
- Gurvich N, Klein PS. Lithium and valproic acid: parallels and contrasts in diverse signaling contexts. *Pharmacol Ther*. 2002; 96:45–66. [PubMed: 12441177]
- Guzzetti S, Calcagno E, Canetta A, Sacchetti G, Fracasso C, Caccia S, et al. Strain differences in paxetine-induced reduction of immobility time in the forced swimming test in mice: role of serotonin. *Eur J Pharmacol*. 2008; 594:117–24. [PubMed: 18691569]

- Hadjipavlou G, Yatham LN. Mood stabilisers in the treatment of bipolar II disorder. *Bipolar II Disord Model Meas Manag*. 2008;120–37.
- Hafen T, Wollnik F. Effect of lithium carbonate on activity level and circadian period in different strains of rats. *Pharmacol Biochem Behav*. 1994; 49:975–83. [PubMed: 7886116]
- Hallcher LM, Sherman WR. The effects of lithium ion and other agents on the activity of *myo*-inositol-1-phosphatase from bovine brain. *J Biol Chem*. 1980; 255:10896–901. [PubMed: 6253491]
- Hammond, WA. A treatise on diseases of the nervous system. New York: D. Appleton and Company; 1871.
- Harvey A. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatry*. 2008; 165:820–9. [PubMed: 18519522]
- Hashimoto R, Hough C, Nakazawa T, Yamamoto T, Chuang DM. Lithium protection against glutamate excitotoxicity in rat cerebral cortical neurons: involvement of NMDA receptor inhibition possibly by decreasing NR2B tyrosine phosphorylation. *J Neurochem*. 2002; 80:589–97. [PubMed: 11841566]
- Haugeto Ø, Ullensvang K, Levy LM, Chaudhry FA, Honoré T, Nielsen M, et al. Brain glutamate transporter proteins form homomultimers. *J Biol Chem*. 1996; 271:27715–22. [PubMed: 8910364]
- Heils A, Teufel A, Petri S, Stöber G, Riederer P, Bengel D, et al. Allelic variation of human serotonin transporter gene expression. *J Neurochem*. 1996; 66:2621–4. [PubMed: 8632190]
- Heit S, Nemeroff CB. Lithium augmentation of antidepressants in treatment-refractory depression. *J Clin Psychiatry*. 1998; 59(Suppl 6):28–33. discussion 4. [PubMed: 9674934]
- Heninger GR, Charney DS, Sternberg DE. Lithium carbonate augmentation of antidepressant treatment. An effective prescription for treatment-refractory depression. *Arch Gen Psychiatry*. 1983; 40:1335–42. [PubMed: 6418110]
- Hilgemann DW, Feng S, Nasuhoglu C. The complex and intriguing lives of PIP2 with ion channels and transporters. *Sci STKE*. 2001 re19-
- Hong C-J, Liou Y-J, Tsai S-J. Effects of BDNF polymorphisms on brain function and behavior in health and disease. *Brain Res Bull*. 2011; 86:287–97. [PubMed: 21924328]
- Huang HC, Klein PS. The Frizzled family: receptors for multiple signal transduction pathways. *Genome Biol*. 2004; 5:234. [PubMed: 15239825]
- Huey LY, Janowsky DS, Judd LL, Abrams A, Parker D, Clopton P. Effects of lithium carbonate on methylphenidate-induced mood, behavior, and cognitive processes. *Psychopharmacology (Berl)*. 1981; 73:161–4. [PubMed: 6785807]
- Jimenez E, Arias B, Mitjans M, Goikolea J, Roda E, Saiz P, et al. Genetic variability at IMPA2, INPP1 and GSK3b increases the risk of suicidal behavior in bipolar patients. 2013
- Johnsson A, Engelmann W, Pflug B, Klemke W. Period lengthening of human circadian rhythms by lithium carbonate, a prophylactic for depressive disorders. *Int J Chronobiol*. 1983; 8:129–47. [PubMed: 6862696]
- Johnsson G. Lithium—early development, toxicity, and renal function. *Neuropsychopharmacology*. 1998; 19:200–5. [PubMed: 9653708]
- Joje RS. Lithium and GSK-3: one inhibitor, two inhibitory actions, multiple outcomes. *Trends Pharmacol Sci*. 2003; 24:441–3. [PubMed: 12967765]
- Kendler K, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. *Arch Gen Psychiatry*. 2005; 62:529–35. [PubMed: 15867106]
- Kim JS, Chang MY, Yu IT, Kim JH, Lee SH, Lee YS, et al. Lithium selectively increases neuronal differentiation of hippocampal neural progenitor cells both in vitro and in vivo. *J Neurochem*. 2004; 89:324–36. [PubMed: 15056276]
- Kim YR, van Meer MP, Tejima E, Murata Y, Mandeville JB, Dai G, et al. Functional MRI of delayed chronic lithium treatment in rat focal cerebral ischemia. *Stroke*. 2008; 39:439–47. [PubMed: 18187690]

- Kirov G, Jones I, McCandless F, Craddock N, Owen M. Family-based association studies of bipolar disorder with candidate genes involved in dopamine neurotransmission: DBH, DAT1, COMT, DRD2, DRD3 and DRD5. *Mol Psychiatry*. 1999; 4:558. [PubMed: 10578238]
- Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci U S A*. 1996; 93:8455–9. [PubMed: 8710892]
- Kovacsics CE, Gottesman II, Gould TD. Lithium's antisuicidal efficacy: elucidation of neurobiological targets using endophenotype strategies. *Annu Rev Pharmacol Toxicol*. 2009; 49:175–98. [PubMed: 18834309]
- Kwok JB, Hallupp M, Loy CT, Chan DK, Woo J, Mellick GD, et al. GSK3B polymorphisms alter transcription and splicing in Parkinson's disease. *Ann Neurol*. 2005; 58:829–39. [PubMed: 16315267]
- Lazarus JH. Lithium and thyroid. *Best Pract Res Clin Endocrinol Metab*. 2009; 23:723–33. [PubMed: 19942149]
- Lee KY, Ahn YM, Joo EJ, Jeong SH, Chang JS, Kim SC, et al. No association of two common SNPs at position –1727 A/T, –50C/T of GSK-3 beta polymorphisms with schizophrenia and bipolar disorder of Korean population. *Neurosci Lett*. 2006; 395:175–8. [PubMed: 16289845]
- Lesch K-P, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*. 1996; 274:1527–31. [PubMed: 8929413]
- Leszczynska-Rodziewicz A, Hauser J, Dmitrzak-Weglarz M, Skibinka M, Czerski P, Zakrzewska A, et al. Lack of association between polymorphisms of dopamine receptors, type D2, and bipolar affective illness in a Polish population. *Med Sci Monit*. 2005; 11:295.
- Li H, Li Q, Du X, Sun Y, Wang X, Kroemer G, et al. Lithium-mediated long-term neuroprotection in neonatal rat hypoxia-ischemia is associated with antiinflammatory effects and enhanced proliferation and survival of neural stem/progenitor cells. *J Cereb Blood Flow Metab*. 2011; 31:2106–15. [PubMed: 21587270]
- Liu P, Ge X, Ding H, Jiang H, Christensen BM, Li J. Role of glutamate decarboxylase-like protein 1 (GADL1) in taurine biosynthesis. *J Biol Chem*. 2012; 287:40898–906. [PubMed: 23038267]
- Logan CY, Nusse R. The Wnt signaling pathway in development and disease. *Annu Rev Cell Dev Biol*. 2004; 20:781–810. [PubMed: 15473860]
- Lohoff FW, Sander T, Ferraro TN, Dahl JP, Gallinat J, Berrettini WH. Confirmation of association between the val66met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and bipolar I disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2005; 139B:51–3. [PubMed: 16152572]
- Loo C, Katalinic N, Mitchell PB, Greenberg B. Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. *J Affect Disord*. 2011; 132:1–13. [PubMed: 20858566]
- Lowther L, Leffert J, Lin A, Umlauf S, Maloney K, Muralidharan A, et al. Increased ratio of anti-apoptotic to pro-apoptotic Bcl2 gene-family members in lithium-responders one month after treatment initiation. *Biol Mood Anxiety Disord*. 2012; 2:1–11. [PubMed: 22738278]
- Lubrich B, Patishi Y, Kofman O, Agam G, Berger M, Belmaker R, et al. Lithium-induced inositol depletion in rat brain after chronic treatment is restricted to the hypothalamus. *Mol Psychiatry*. 1997; 2:407. [PubMed: 9322236]
- Mamelak M. An amphetamine model of manic depressive illness. *Int Pharmacopsychiatr*. 1978; 13:193–208.
- Manchia M, Adli M, Akula N, Ardu R, Aubry J-M, Backlund L, et al. Assessment of response to lithium maintenance treatment in bipolar disorder: a consortium on lithium genetics (ConLiGen) report. *PLoS ONE*. 2013; 8:e65636. [PubMed: 23840348]
- Manchia M, Congiu D, Squassina A, Lampus S, Ardu R, Chillotti C, et al. No association between lithium full responders and the DRD1, DRD2, DRD3, DAT1, 5-HTTLPR and HTR2A genes in a Sardinian sample. *Psychiatry Res*. 2009a; 169:164–6. [PubMed: 19647327]
- Manchia M, Squassina A, Congiu D, Chillotti C, Ardu R, Severino G, et al. Interacting genes in lithium prophylaxis: preliminary results of an exploratory analysis on the role of DGKH and

- NR1D1 gene polymorphisms in 199 Sardinian bipolar patients. *Neurosci Lett*. 2009b; 467:67–71. [PubMed: 19818381]
- Manji HK, Lenox RH. Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. *Biol Psychiatry*. 1999; 46:1328–51. [PubMed: 10578449]
- Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry*. 2000; 48:740–54. [PubMed: 11063971]
- Mann L, Heldman E, Bersudsky Y, Vatner SF, Ishikawa Y, Almog O, et al. Inhibition of specific adenylyl cyclase isoforms by lithium and carbamazepine, but not valproate, may be related to their antidepressant effect. *Bipolar Disord*. 2009; 11:885–96. [PubMed: 19922557]
- Mann L, Heldman E, Shaltiel G, Belmaker RH, Agam G. Lithium preferentially inhibits adenylyl cyclase V and VII isoforms. *Int J Neuropsychopharmacol*. 2008; 11:533–9. [PubMed: 18205980]
- Mansour H, Wood J, Logue T, Chowdari K, Dayal M, Kupfer D, et al. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. *Genes Brain Behav*. 2006; 5:150–7. [PubMed: 16507006]
- Martucci L, Wong AHC, De Luca V, Likhodi O, Wong GWH, King N, et al. N-methyl-D-aspartate receptor NR2B subunit gene GRIN2B in schizophrenia and bipolar disorder: polymorphisms and mRNA levels. *Schizophr Res*. 2006; 84:214–21. [PubMed: 16549338]
- Masui T, Hashimoto R, Kusumi I, Suzuki K, Tanaka T, Nakagawa S, et al. Lithium response and val66met polymorphism of the brain-derived neurotrophic factor gene in Japanese patients with bipolar disorder. *Psychiatr Genet*. 2006; 16:49–50. [PubMed: 16538178]
- McCarthy MJ, Nievergelt CM, Shekhtman T, Kripke DF, Welsh DK, Kelsoe JR. Functional genetic variation in the Rev-Erba pathway and lithium response in the treatment of bipolar disorder. *Genes Brain Behav*. 2011; 10:852–61. [PubMed: 21781277]
- McEachron DL, Kripke DF, Wyborney VG. Lithium promotes entrainment of rats to long circadian light–dark cycles. *Psychiatry Res*. 1981; 5:1–9. [PubMed: 6792648]
- McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet*. 2012; 379:721–8. [PubMed: 22265699]
- Mendlewicz J, Fieve RR, Stallone F. Relationship between the effectiveness of lithium therapy and family history. *Am J Psychiatry*. 1973; 130:1011–3. [PubMed: 4580440]
- Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld R, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007; 64:543. [PubMed: 17485606]
- Michelon L, Meira-Lima I, Cordeiro Q, Miguita K, Breen G, Collier D, et al. Association study of the INPP1, 5HTT, BDNF, AP-2 β and *GSK-3 β* gene variants and retrospectively scored response to lithium prophylaxis in bipolar disorder. *Neurosci Lett*. 2006; 403:288–93. [PubMed: 16787706]
- Minadeo N, Layden B, Amari LV, Thomas V, Radloff K, Srinivasan C, et al. Effect of Li⁺ upon the Mg²⁺-dependent activation of recombinant G α 1. *Arch Biochem Biophys*. 2001; 388:7–12. [PubMed: 11361143]
- Mitchell PB, Hadzi-Pavlovic D. Lithium treatment for bipolar disorder. *Bull World Health Organ*. 2000; 78:515–7. [PubMed: 10885179]
- Molendijk ML, Bus BAA, Spinhoven P, Kaimatzoglou A, Voshaar RCO, Penninx BWJH, et al. A systematic review and meta-analysis on the association between BDNF val66met and hippocampal volume — a genuine effect or a winners curse? *Am J Med Genet B Neuropsychiatr Genet*. 2012; 159B:731–40. [PubMed: 22815222]
- Montag C, Basten U, Stelzel C, Fiebach CJ, Reuter M. The BDNF val66met polymorphism and anxiety: support for animal knock-in studies from a genetic association study in humans. *Psychiatry Res*. 2010; 179:86–90. [PubMed: 20478625]
- Moore GJ, Bebachuk JM, Parrish JK, Faulk MW, Arfken CL, Strahl-Bevacqua J, et al. Temporal dissociation between lithium-induced changes in frontal lobe *myo*-inositol and clinical response in manic-depressive illness. *Am J Psychiatry*. 1999; 156:1902–8. [PubMed: 10588403]
- Mørk A. Effects of lithium treatment on extracellular serotonin levels in the dorsal hippocampus and wet-dog shakes in the rat. *Eur Neuropsychopharmacol*. 1998; 8:267–72. [PubMed: 9928915]

- Mørk A, Geisler A. Effects of lithium ex vivo on the GTP-mediated inhibition of calcium-stimulated adenylate cyclase activity in rat brain. *Eur J Pharmacol.* 1989; 168:347–54. [PubMed: 2583240]
- Mota de Freitas D, Castro MMCA, Geraldes CFGC. Is competition between Li^+ and Mg^{2+} the underlying theme in the proposed mechanisms for the pharmacological action of lithium salts in bipolar disorder? *Acc Chem Res.* 2006; 39:283–91. [PubMed: 16618096]
- Mueller A, Armbruster D, Moser DA, Canli T, Lesch K-P, Brocke B, et al. Interaction of serotonin transporter gene-linked polymorphic region and stressful life events predicts cortisol stress response. *Neuropsychopharmacology.* 2011; 36:1332–9. [PubMed: 21368747]
- Müller DJ, De Luca V, Sicard T, King N, Strauss J, Kennedy JL. Brain-derived neurotrophic factor (BDNF) gene and rapid-cycling bipolar disorder: family-based association study. *Br J Psychiatry.* 2006; 189:317–23. [PubMed: 17012654]
- Muraki I, Inoue T, Hashimoto S, Izumi T, Ito K, Koyama T. Effect of subchronic lithium treatment on citalopram-induced increases in extracellular concentrations of serotonin in the medial prefrontal cortex. *J Neurochem.* 2001; 76:490–7. [PubMed: 11208912]
- Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012; 380:2197–223. [PubMed: 23245608]
- Neves-Pereira M, Mundo E, Muglia P, King N, Maciardi F, Kennedy JL. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. *Am J Hum Genet.* 2002; 71:651–5. [PubMed: 12161822]
- Newman ME, Belmaker RH. Effects of lithium in vitro and ex vivo on components of the adenylate cyclase system in membranes from the cerebral cortex of the rat. *Neuropharmacology.* 1987; 26:211–7. [PubMed: 3035412]
- Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, et al. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2006; 141B:234–41. [PubMed: 16528748]
- Nissen S, Liang S, Shekhtman T, Kelsoe JR. Evidence for association of bipolar disorder to haplotypes in the 22q12.3 region near the genes stargazin, *ift27* and parvalbumin. *Am J Med Genet B Neuropsychiatr Genet.* 2012; 159B:941–50. [PubMed: 23038240]
- Nonaka S, Hough CJ, Chuang DM. Chronic lithium treatment robustly protects neurons in the central nervous system against excitotoxicity by inhibiting N-methyl-D-aspartate receptor-mediated calcium influx. *Proc Natl Acad Sci U S A.* 1998; 95:2642–7. [PubMed: 9482940]
- O'Brien WT, Harper AD, Jove F, Woodgett JR, Maretto S, Piccolo S, et al. Glycogen synthase kinase-3 β haploinsufficiency mimics the behavioral and molecular effects of lithium. *J Neurosci.* 2004; 24:6791–8. [PubMed: 15282284]
- O'Donnell T, Rotzinger S, Nakashima TT, Hanstock CC, Ulrich M, Silverstone PH. Chronic lithium and sodium valproate both decrease the concentration of *myo*-inositol and increase the concentration of inositol monophosphates in rat brain. *Brain Res.* 2000; 880:84–91. [PubMed: 11032992]
- Ohnishi T, Watanabe A, Ohba H, Iwayama Y, Maekawa M, Yoshikawa T. Behavioral analyses of transgenic mice harboring bipolar disorder candidate genes, IMPA1 and IMPA2. *Neurosci Res.* 2010; 67:86–94. [PubMed: 20153384]
- Okamoto Y, Motohashi N, Hayakawa H, Muraoka M, Yamawaki S. Addition of lithium to chronic antidepressant treatment potentiates presynaptic serotonergic function without changes in serotonergic receptors in the rat cerebral cortex. *Neuropsychobiology.* 1996; 33:17–20. [PubMed: 8821370]
- Ollila HM, Soronen P, Silander K, Palo OM, Kieseppa T, Kaunisto MA, et al. Findings from bipolar disorder genome-wide association studies replicate in a Finnish bipolar family-cohort. *Mol Psychiatry.* 2009; 14:351–3. [PubMed: 19308021]
- Omata N, Chiu CT, Moya PR, Leng Y, Wang Z, Hunsberger JG, et al. Lentivirally mediated GSK-3 β silencing in the hippocampal dentate gyrus induces antidepressant-like effects in stressed mice. 2011
- Omata N, Murata T, Takamatsu S, Maruoka N, Mitsuya H, Yonekura Y, et al. Neuroprotective effect of chronic lithium treatment against hypoxia in specific brain regions with upregulation of cAMP

response element binding protein and brain-derived neurotrophic factor but not nerve growth factor: comparison with acute lithium treatment. *Bipolar Disord.* 2008; 10:360–8. [PubMed: 18402624]

- Osten P, Stern-Bach Y. Learning from stargazin: the mouse, the phenotype and the unexpected. *Curr Opin Neurobiol.* 2006; 16:275–80. [PubMed: 16678401]
- Patel NC, DelBello MP, Cecil KM, Adler CM, Bryan HS, Stanford KE, et al. Lithium treatment effects on *myo*-inositol in adolescents with bipolar depression. *Biol Psychiatry.* 2006; 60:998–1004. [PubMed: 17056394]
- Perlis RH, Smoller JW, Ferreira MAR, McQuillin A, Bass N, Lawrence J, et al. A genomewide association study of response to lithium for prevention of recurrence in bipolar disorder. *Am J Psychiatry.* 2009; 166:718–25. [PubMed: 19448189]
- Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, et al. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J Neurosci.* 2004; 24:10099–102. [PubMed: 15537879]
- Phiel CJ, Klein PS. Molecular targets of lithium action. *Annu Rev Pharmacol Toxicol.* 2001; 41:789–813. [PubMed: 11264477]
- Piccardi MP, Ardu R, Chillotti C, Deleuze JF, Mallet J, Meloni R, et al. Manic-depressive illness: an association study with the inositol polyphosphate 1-phosphatase and serotonin transporter genes. *Psychiatr Genet.* 2002; 12:23–7. [PubMed: 11901356]
- Pollock BG, Ferrell RE, Mulsant BH, Mazumdar S, Miller M, Sweet RA, et al. Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. *Neuropsychopharmacology.* 2000; 23:587–90. [PubMed: 11027924]
- Polter A, Beurel E, Yang S, Garner R, Song L, Miller CA, et al. Deficiency in the inhibitory serine-phosphorylation of glycogen synthase kinase-3 increases sensitivity to mood disturbances. *Neuropsychopharmacology.* 2010; 35:1761–74. [PubMed: 20357757]
- Polter A, Li X. Glycogen synthase kinase-3 is an intermediate modulator of serotonin neurotransmission. *Front Mol Neurosci.* 2011; 4. [PubMed: 21430823]
- Possidente B, Exner RH. Gene-dependent effect of lithium on circadian rhythms in mice (*Mus musculus*). *Chronobiol Int.* 1986; 3:17–21. [PubMed: 3677192]
- Preitner N, Damiola F, Luis Lopez M, Zakany J, Duboule D, Albrecht U, et al. The orphan nuclear receptor REV-ERB α controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell.* 2002; 110:251–60. [PubMed: 12150932]
- Prickaerts J, Moechars D, Cryns K, Lenaerts I, van Craenendonck H, Goris I, et al. Transgenic mice overexpressing glycogen synthase kinase 3 β : a putative model of hyperactivity and mania. *J Neurosci.* 2006; 26:9022–9. [PubMed: 16943560]
- Rej S, Herrmann N, Shulman K. The effects of lithium on renal function in older adults — a systematic review. *J Geriatr Psychiatry Neurol.* 2012; 25:51–61. [PubMed: 22467847]
- Roybal K, Theobald D, Graham A, DiNieri JA, Russo SJ, Krishnan V, et al. Mania-like behavior induced by disruption of CLOCK. *Proc Natl Acad Sci.* 2007; 104:6406–11. [PubMed: 17379666]
- Russ C, Lovestone S, Powell JF. Identification of sequence variants and analysis of the role of the glycogen synthase kinase 3 β gene and promoter in late onset Alzheimer's disease. *Mol Psychiatry.* 2001; 6:320–4. [PubMed: 11326302]
- Rybakowski J, Dmitrzak-Weglarz M, Suwalska A, Leszczynska-Rodziewicz A, Hauser J. Dopamine D1 receptor gene polymorphism is associated with prophylactic lithium response in bipolar disorder. *Pharmacopsychiatry.* 2009; 42:20. [PubMed: 19153942]
- Rybakowski J, Suwalska A, Skibinska M, Szczepankiewicz A, Leszczynska-Rodziewicz A, Permoda A, et al. Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. *Pharmacopsychiatry.* 2005a; 38:166–70. [PubMed: 16025419]
- Rybakowski JK. Genetic influences on response to mood stabilizers in bipolar disorder. *CNS Drug.* 2013; 1–9.
- Rybakowski JK, Suwalska A, Czerski PM, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Hauser J. Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. *Pharmacol Rep.* 2005b; 57:124–7. [PubMed: 15849387]

- Ryves WJ, Harwood AJ. Lithium inhibits glycogen synthase kinase-3 by competition for magnesium. *Biochem Biophys Res Commun.* 2001; 280:720–5. [PubMed: 11162580]
- Salter MW, Kalia LV. Src kinases: a hub for NMDA receptor regulation. *Nat Rev Neurosci.* 2004; 5:317–28. [PubMed: 15034556]
- Schloesser RJ, Martinowich K, Manji HK. Mood-stabilizing drugs: mechanisms of action. *Trends Neurosci.* 2012; 35:36–46. [PubMed: 22217451]
- Schou M. Long-lasting neurological sequelae after lithium intoxication. *Acta Psychiatr Scand.* 1984; 70:594–602. [PubMed: 6524425]
- Schou M. Lithium treatment at 52. *J Affect Disord.* 2001; 67:21–32. [PubMed: 11869750]
- Schou M, Amdisen A, Trap-Jensen J. Lithium poisoning. *Am J Psychiatry.* 1968; 125:520–7. [PubMed: 5711814]
- Schulze TG. Genetic research into bipolar disorder: the need for a research framework that integrates sophisticated molecular biology and clinically-informed phenotype characterization. *Psychiatr Clin N Am.* 2010; 33:67.
- Schulze TG, Alda M, Adli M, Akula N, Arda R, Bui ET, et al. The International Consortium on Lithium Genetics (ConLiGen): an initiative by the NIMH and IGSLI to study the genetic basis of response to lithium treatment. *Neuropsychobiology.* 2010; 62:72–8. [PubMed: 20453537]
- Schulze TG, Hardy J, McMahon FJ. Inconsistent designs of association studies: a missed opportunity. *Mol Psychiatry.* 2003; 8:770–2. [PubMed: 12931204]
- Sears C, Markie D, Olds R, Fitches A. Evidence of associations between bipolar disorder and the brain-derived neurotrophic factor (BDNF) gene. *Bipolar Disord.* 2011; 13:630–7. [PubMed: 22085476]
- Senatorov VV, Ren M, Kanai H, Wei H, Chuang DM. Short-term lithium treatment promotes neuronal survival and proliferation in rat striatum infused with quinolinic acid, an excitotoxic model of Huntington's disease. *Mol Psychiatry.* 2003; 9:371–85. [PubMed: 14702090]
- Serretti A, Benedetti F, Mandelli L, Lorenzi C, Pirovano A, Colombo C, et al. Genetic dissection of psychopathological symptoms: insomnia in mood disorders and *CLOCK* gene polymorphism. *Am J Med Genet B Neuropsychiatr Genet.* 2003; 121:35–8. [PubMed: 12898572]
- Serretti A, Cusin C, Benedetti F, Mandelli L, Pirovano A, Zanardi R, et al. Insomnia improvement during antidepressant treatment and *CLOCK* gene polymorphism. *Am J Med Genet B Neuropsychiatr Genet.* 2005; 137B:36–9. [PubMed: 15952199]
- Serretti A, Lilli R, Lorenzi C, Franchini L, Di Bella D, Catalano M, et al. Dopamine receptor D2 and D4 genes, GABAA alpha-1 subunit gene and response to lithium prophylaxis in mood disorders. *Psychiatry Res.* 1999a; 87:7–19. [PubMed: 10512150]
- Serretti A, Lilli R, Lorenzi C, Franchini L, Smeraldi E. Dopamine receptor D3 gene and response to lithium prophylaxis in mood disorders. *Int J Neuropsychopharmacol.* 1998; 1:125–9. [PubMed: 11281956]
- Serretti A, Lilli R, Lorenzi C, Gasperini M, Smeraldi E. Tryptophan hydroxylase gene and response to lithium prophylaxis in mood disorders. *J Psychiatr Res.* 1999b; 33:371–7. [PubMed: 10504005]
- Serretti A, Lilli R, Mandelli L, Lorenzi C, Smeraldi E. Serotonin transporter gene associated with lithium prophylaxis in mood disorders. *Pharmacogenomics J.* 2001; 1:71–7. [PubMed: 11913731]
- Serretti A, Lorenzi C, Lilli R, Mandelli L, Pirovano A, Smeraldi E. Pharmacogenetics of lithium prophylaxis in mood disorders: analysis of COMT, MAO-A, and Gβ3 variants. *Am J Med Genet.* 2002; 114:370–9. [PubMed: 11992559]
- Serretti A, Lorenzi C, Lilli R, Smeraldi E. Serotonin receptor 2A, 2C, 1A genes and response to lithium prophylaxis in mood disorders. *J Psychiatr Res.* 2000; 34:89–98. [PubMed: 10758249]
- Serretti A, Malitas PN, Mandelli L, Lorenzi C, Ploia C, Alevizos B, et al. Further evidence for a possible association between serotonin transporter gene and lithium prophylaxis in mood disorders. *Pharmacogenomics J.* 2004; 4:267–73. [PubMed: 15111989]
- Severino G, Congiu D, Serreli C, De Lisa R, Chillotti C, Del Zompo M, et al. A48G polymorphism in the D1 receptor genes associated with bipolar I disorder. *Am J Med Genet B Neuropsychiatr Genet.* 2005; 134:37–8. [PubMed: 15704231]

- Shaldubina A, Buccafusca R, Johanson RA, Agam G, Belmaker RH, Berry GT, et al. Behavioural phenotyping of sodium-*myo*-inositol cotransporter heterozygous knockout mice with reduced brain inositol. *Genes Brain Behav.* 2007; 6:253–9. [PubMed: 16848785]
- Shaldubina A, Johanson RA, O'Brien WT, Buccafusca R, Agam G, Belmaker RH, et al. SMIT1 haploinsufficiency causes brain inositol deficiency without affecting lithium-sensitive behavior. *Mol Genet Metab.* 2006; 88:384–8. [PubMed: 16644257]
- Sherman WR, Leavitt AL, Honchar MP, Hallcher LM, Phillips BE. Evidence that lithium alters phosphoinositide metabolism: chronic administration elevates primarily D-*myo*-inositol-1-phosphate in cerebral cortex of the rat. *J Neurochem.* 1981; 36:1947–51. [PubMed: 6264039]
- Shi J, Wittke-Thompson JK, Badner JA, Hattori E, Potash JB, Willour VL, et al. *CLOCK* genes may influence bipolar disorder susceptibility and dysfunctional circadian rhythm. *Am J Med Genet B Neuropsychiatr Genet.* 2008; 147B:1047–55. [PubMed: 18228528]
- Shim S, Hammonds M, Mervis R. Four weeks lithium treatment alters neuronal dendrites in the rat hippocampus. *Int J Neuropsychopharmacol.* 2013;1. official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP).
- Silberberg G, Levit A, Collier D, St Clair D, Munro J, Kerwin RW, et al. Stargazin involvement with bipolar disorder and response to lithium treatment. *Pharmacogenet Genomics.* 2008; 18:403–12. [<http://dx.doi.org/10.1097/FPC.0b013e3282f974ca>]. [PubMed: 18408563]
- Silverstone PH, McGrath BM. Lithium and valproate and their possible effects on the *myo*-inositol second messenger system in healthy volunteers and bipolar patients. *Int Rev Psychiatry.* 2009; 21:414–23. [PubMed: 20374155]
- Simard M, Gumbiner B, Lee A, Lewis H, Norman D. Lithium carbonate intoxication: a case report and review of the literature. *Arch Intern Med.* 1989; 149:36–46. [PubMed: 2492186]
- Sjoholt G, Ebstein RP, Lie RT, Berle JO, Mallet J, Deleuze JF, et al. Examination of IMPA1 and IMPA2 genes in manic-depressive patients: association between IMPA2 promoter polymorphisms and bipolar disorder. *Mol Psychiatry.* 2003; 9:621–9. [PubMed: 14699425]
- Sklar P, Gabriel S, McInnis M, Bennett P, Lim Y, Tsan G, et al. Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. *Mol Psychiatry.* 2002; 7:579–93. [PubMed: 12140781]
- Smeraldi E, Petroccione A, Gasperini M, Macciardi F, Orsini A, Kidd KK. Outcomes on lithium treatment as a tool for genetic studies in affective disorders. *J Affect Disord.* 1984; 6:139–51. [PubMed: 6233346]
- Smeraldi E, Zanardi R, Benedetti F, Di Bella D, Perez J, Catalano M. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Mol Psychiatry.* 1998; 3:508. [PubMed: 9857976]
- Smith EN, Bloss CS, Badner JA, Barrett T, Belmonte PL, Berrettini W, et al. Genome-wide association study of bipolar disorder in European American and African American individuals. *Mol Psychiatry.* 2009; 14:755–63. [PubMed: 19488044]
- Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet.* 2003; 123C:48–58. [PubMed: 14601036]
- Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science.* 2010; 327:863–6. [PubMed: 20075215]
- Soria V, Martinez-Amoros E, Escaramis G, Valero J, Perez-Egea R, Garcia C, et al. Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. *Neuropsychopharmacology.* 2010; 35:1279–89. [PubMed: 20072116]
- Spiegelberg BD, Xiong JP, Smith JJ, Gu RF, York JD. Cloning and characterization of a mammalian lithium-sensitive bisphosphate 3'-nucleotidase inhibited by inositol 1,4-bisphosphate. *J Biol Chem.* 1999; 274:13619–28. [PubMed: 10224133]
- Squassina A, Manchia M, Congiu D, Severino G, Chillotti C, Ardu R, et al. The diacylglycerol kinase eta gene and bipolar disorder: a replication study in a Sardinian sample. *Mol Psychiatry.* 2009; 14:350–1. [PubMed: 19308020]

- Srinivasan C, Toon J, Amari L, Abukhdeir AM, Hamm H, Gerald CF, et al. Competition between lithium and magnesium ions for the G-protein transducin in the guanosine 5'-diphosphate bound conformation. *J Inorg Biochem.* 2004; 98:691–701. [PubMed: 15134914]
- Stambolic V, Ruel L, Woodgett JR. Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signalling in intact cells. *Curr Biol.* 1996; 6:1664–8. [PubMed: 8994831]
- Stamm TJ, Adli M, Kirchheiner J, Smolka MN, Kaiser R, Tremblay PB, et al. Serotonin transporter gene and response to lithium augmentation in depression. *Psychiatr Genet.* 2008; 18:92–7. [PubMed: 18349701]
- Steen VM, Lovlie R, Osher Y, Belmaker RH, Berle JO, Gulbrandsen A-K. The polymorphic ino-sitol polyphosphate 1-phosphatase gene as a candidate for pharmacogenetic prediction of lithium-responsive manic-depressive illness. *Pharmacogenetics.* 1998; 8:259–68. [PubMed: 9682271]
- Stevens A, Fischer A, Bartels M, Buchkremer G. Electroconvulsive therapy: a review on indications, methods, risks and medication. *Eur Psychiatry.* 1996; 11:165–74. [PubMed: 19698445]
- Strober M, Morrell W, Burroughs J, Lampert C, Danforth H, Freeman R. A family study of bipolar I disorder in adolescence: early onset of symptoms linked to increased familial loading and lithium resistance. *J Affect Disord.* 1988; 15:255–68. [PubMed: 2975298]
- Szczepankiewicz A, Rybakowski JK, Suwalska A, Skibinska M, Leszczynska-Rodziewicz A, Dmistrz-Weglarz M, et al. Association study of the glycogen synthase kinase-3 β gene polymorphism with prophylactic lithium response in bipolar patients. *World J Biol Psychiatry.* 2006; 7:158–61. [PubMed: 16861141]
- Szczepankiewicz A, Skibinska M, Suwalska A, Hauser J, Rybakowski JK. The association study of three FYN polymorphisms with prophylactic lithium response in bipolar patients. *Hum Psychopharmacol Clin Exp.* 2009a; 24:287–91.
- Szczepankiewicz A, Skibińska M, Suwalska A, Hauser J, Rybakowski JK. No association of three GRIN2B polymorphisms with lithium response in bipolar patients. *Pharmacol Rep.* 2009b; 61:448. [PubMed: 19605943]
- Szeszko PR, Lipsky R, Mentschel C, Robinson D, Gunduz-Bruce H, Sevy S, et al. Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Mol Psychiatry.* 2005; 10:631–6. [PubMed: 15768049]
- Takata A, Kawasaki H, Iwayama Y, Yamada K, Gotoh L, Mitsuyasu H, et al. Nominal association between a polymorphism in DGKH and bipolar disorder detected in a meta-analysis of East Asian case-control samples. *Psychiatry Clin Neurosci.* 2011; 65:280–5. [PubMed: 21507135]
- Tesli M, Kähler AK, Andreassen BK, Werge T, Mors O, Mellerup E, et al. No association between DGKH and bipolar disorder in a Scandinavian case-control sample. *Psychiatr Genet.* 2009; 19:269. [PubMed: 19478689]
- Tharoor H, Kotambail A, Jain S, Sharma PSVN, Satyamoorthy K. Study of the association of serotonin transporter triallelic 5-HTTLPR and STin2 VNTR polymorphisms with lithium prophylaxis response in bipolar disorder. *Psychiatr Genet.* 2013; 23:77–81. [PubMed: 23277128]
- Toker L, Belmaker RH, Agam G. Gene-expression studies in understanding the mechanism of action of lithium. *Expert Rev Neurother.* 2011; 12:93–7. [PubMed: 22243047]
- Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Ahrens B, et al. MAOA: association and linkage studies with lithium responsive bipolar disorder. *Psychiatr Genet.* 1999a; 9:13–6. [PubMed: 10335547]
- Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Martin R, et al. Lithium responsive bipolar disorder, unilinearity, and chromosome 18: a linkage study. *Am J Med Genet.* 1999b; 88:411–5. [PubMed: 10402510]
- Turecki G, Grof P, Grof E, D'souza V, Lebus L, Marineau C, et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. *Mol Psychiatry.* 2001; 6:570. [PubMed: 11526471]
- Urs NM, Snyder JC, Jacobsen JPR, Peterson SM, Caron MG. Deletion of *GSK3 β* in D2R-expressing neurons reveals distinct roles for β -arrestin signaling in antipsychotic and lithium action. *Proc Natl Acad Sci.* 2012; 109:20732–7. [PubMed: 23188793]

- van Kammen DP, Docherty JP, Marder SR, Rosenblatt JE, Bunney WE Jr. Lithium attenuates the activation-euphoria but not the psychosis induced by D-amphetamine in schizophrenia. *Psychopharmacology (Berl)*. 1985; 87:111–5. [PubMed: 3933028]
- Vincze I, Perroud N, Buresi C, Baud P, Bellivier F, Etain B, et al. Association between brain3 derived neurotrophic factor gene and a severe form of bipolar disorder, but no interaction with the serotonin transporter gene. *Bipolar Disord*. 2008; 10:580–7. [PubMed: 18657242]
- Walther DJ, Peter J-U, Bashammakh S, Hörtnagl H, Voits M, Fink H, et al. Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science*. 2003; 299:76. [PubMed: 12511643]
- Wang Z, Fan J, Gao K, Li Z, Yi Z, Wang L, et al. Neurotrophic tyrosine kinase receptor type 2 (NTRK2) gene associated with treatment response to mood stabilizers in patients with bipolar I disorder. *J Mol Neurosci*. 2013; 50:305–10. [PubMed: 23315174]
- Wang Z, Li Z, Chen J, Huang J, Yuan C, Hong W, et al. Association of BDNF gene polymorphism with bipolar disorders in Han Chinese population. *Genes Brain Behav*. 2012; 11:524–8. [PubMed: 22548711]
- Weber H, Kittel-Schneider S, Gessner A, Domschke K, Neuner M, Jacob CP, et al. Cross-disorder analysis of bipolar risk genes: further evidence of DGKH as a risk gene for bipolar disorder, but also unipolar depression and adult ADHD. *Neuropsychopharmacology*. 2011; 36:2076–85. [PubMed: 21654738]
- Wegener G, Bandpey Z, Heiberg I, Mørk A, Rosenberg R. Increased extracellular serotonin level in rat hippocampus induced by chronic citalopram is augmented by subchronic lithium: neurochemical and behavioural studies in the rat. *Psychopharmacology*. 2003; 166:188–94. [PubMed: 12552361]
- Welsh DK, Moore-Ede MC. Lithium lengthens circadian period in a diurnal primate *Saimiri sciureus*. *Biol Psychiatry*. 1990; 28:117–26. [PubMed: 2116188]
- Werneke U, Ott M, Renberg ES, Taylor D, Stegmayr B. A decision analysis of long-term lithium treatment and the risk of renal failure. *Acta Psychiatr Scand*. 2012; 126:186–97. [PubMed: 22404233]
- Wexler EM, Geschwind DH, Palmer TD. Lithium regulates adult hippocampal progenitor development through canonical Wnt pathway activation. *Mol Psychiatry*. 2008; 13:285–92. [PubMed: 17968353]
- Williams RS, Cheng L, Mudge AW, Harwood AJ. A common mechanism of action for three mood-stabilizing drugs. *Nature*. 2002; 417:292–5. [PubMed: 12015604]
- Wolf FI, Cittadini A. Chemistry and biochemistry of magnesium. *Mol Asp Med*. 2003; 24:3–9.
- Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, Golshan S, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol Psychiatry*. 2009; 66:298–301. [PubMed: 19358978]
- Xu F, Plummer MR, Len G-W, Nakazawa T, Yamamoto T, Black IB, et al. Brain-derived neurotrophic factor rapidly increases NMDA receptor channel activity through Fyn-mediated phosphorylation. *Brain Res*. 2006; 1121:22–34. [PubMed: 17045972]
- Yin L, Wang J, Klein PS, Lazar MA. Nuclear receptor Rev-erb α is a critical lithium-sensitive component of the circadian clock. *Science*. 2006; 311:1002–5. [PubMed: 16484495]
- York JD, Ponder JW, Majerus PW. Definition of a metal-dependent/Li(+)-inhibited phosphomonoesterase protein family based upon a conserved three-dimensional core structure. *Proc Natl Acad Sci U S A*. 1995; 92:5149–53. [PubMed: 7761465]
- Yoshida K, Ito K, Sato K, Takahashi H, Kamata M, Higuchi H, et al. Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2002; 26:383–6.
- Yu F, Wang Z, Tanaka M, Chiu C-T, Leeds P, Zhang Y, et al. Posttrauma cotreatment with lithium and valproate: reduction of lesion volume, attenuation of blood–brain barrier disruption, and improvement in motor coordination in mice with traumatic brain injury: laboratory investigation. *J Neurosurg*. 2013; 119:766–73. [PubMed: 23848820]
- Yu F, Wang Z, Tchantchou F, Chiu C-T, Zhang Y, Chuang D-M. Lithium ameliorates neurodegeneration, suppresses neuroinflammation, and improves behavioral performance in a mouse model of traumatic brain injury. *J Neurotrauma*. 2012; 29:362–74. [PubMed: 21895523]

- Zalsman G, Huang Y-y, Oquendo M, Burke A, Hu X-z, Brent D, et al. Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. *Am J Psychiatry*. 2006; 163:1588–93. [PubMed: 16946185]
- Zanardi R, Benedetti F, Di Bella D, Catalano M, Smeraldi E. Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *J Clin Psychopharmacol*. 2000; 20:105–7. [PubMed: 10653220]
- Zeng Z, Wang T, Li T, Li Y, Chen P, Zhao Q, et al. Common SNPs and haplotypes in DGKH are associated with bipolar disorder and schizophrenia in the Chinese Han population. *Mol Psychiatry*. 2011; 16:473–5. [PubMed: 20733578]
- Zhang F, Phiel CJ, Spece L, Gurvich N, Klein PS. Inhibitory phosphorylation of glycogen synthase kinase-3 (GSK-3) in response to lithium. Evidence for autoregulation of GSK-3. *J Biol Chem*. 2003; 278:33067–77. [PubMed: 12796505]
- Zhang K, Song X, Xu Y, Li X, Liu P, Sun N, et al. Continuous *GSK-3 β* overexpression in the hippocampal dentate gyrus induces prodepressant-like effects and increases sensitivity to chronic mild stress in mice. *J Affect Disord*. 2012; 146(1):45–52. [PubMed: 23021826]

Table 1

Human pharmacogenetic studies related to direct enzyme targets of lithium and lithium therapy response. BD, bipolar disorder; SNP, single nucleotide polymorphism; PTSD, post-traumatic stress disorder.

Gene and marker	Subjects	Finding	Reference
Phosphoinositide signaling pathway			
<i>INPP1</i> , A682G, G153T, G348A, C973A	BD patients, European (10M, 13F); Israeli sample (N = 54)	C973A SNP was associated with lithium response.	Steen et al. (1998)
<i>IMPA1</i> , <i>IMPA2</i> , multiple SNPs	BD patients, European (N = 44)	No association with lithium response	Sjoholt et al. (2003)
<i>INPP1</i> , C973A	BD patients, mixed backgrounds mostly Caucasian (43M, 91F)	No association with lithium response	Michelon et al. (2006)
<i>IMPA1</i> , <i>IMPA2</i> , <i>INPP1</i> multiple SNPs	BD patients and patients with schizoaffective disorder, bipolar type, Caucasian (184)	Significant interaction between lithium response and rs2064721 of <i>INPP1</i> gene and PTSD	Bremer et al. (2007)
<i>DGKH</i> , rs9315885, rs1012053, rs1170191	BD patients, European (59M, 140F)	No association with lithium response	Manchia et al. (2009)
GSK-3			
<i>GSK-3β</i> , rs334558 (−50 T/C)	BD patients, European origin (27M, 61F)	C allele carriers of the SNP showed more improvement after lithium treatment.	Benedetti et al. (2005)
<i>GSK-3β</i> , A1727T	BD patients, mixed backgrounds mostly Caucasian (43M, 91F)	No association with lithium response	Michelon et al. (2006)
<i>GSK-3β</i> , rs334558	BD patients (41M, 48F)	No association with lithium response	Szczepankiewicz et al. (2006)
<i>GSK-3β</i> , rs334558	BD/unipolar depression patients mixed, European (35M, 46F)	Carriers of the C allele were associated with a better lithium augmentation of antidepressant treatment.	Adli et al. (2007)
<i>GSK-3β</i> , multiple SNPs	BD patients and patients with schizoaffective disorder, bipolar type, Caucasian (184)	Association between rs2199503 and lithium response in patients with PTSD	Bremer et al. (2007)
<i>GSK-3β</i> , rs6438552	BD patients, Caucasian (N = 282)	Trend toward association with lithium response	McCarthy et al. (2011)

Table 2

Human pharmacogenetic studies of genes related to neurotrophic and neuroprotective functions and lithium therapy response. BD, bipolar disorder; SNP, single nucleotide polymorphism; PTSD, post-traumatic stress disorder.

Gene and marker	Subjects	Finding	Reference
<i>BDNF</i> , rs6265 (val66met), -270 C/T	BD patients, European (35M, 53F)	rs6265 SNP was associated with lithium response. Trend for association between 270C/T SNP and lithium response	Rybakowski et al. (2005)
<i>BDNF</i> , rs6265	BD patients, Japanese (76M, 85F)	No association with lithium response	Masui et al. (2006)
<i>BDNF</i> , rs6265	BD patients, mixed backgrounds, mostly Caucasian (43M, 91F)	No association with lithium response	Michelon et al. (2006)
<i>BDNF</i> , <i>NTRK2</i> (multiple SNPs)	BD patients and patients with schizoaffective disorder, bipolar type, Caucasian (184)	rs1387923 and rs1565445 of <i>NTRK2</i> were associated with lithium response when patients were stratified according to other clinical diagnoses like PTSD and suicidal ideation.	Bremer et al. (2007)
<i>BDNF</i> , rs6265, rs2030324, rs988748; <i>NTRK2</i> , rs1187327, rs1187326, rs2289656	BD patients, European (42M, 66F)	Associations between SNPs of <i>BDNF</i> , rs6265 and rs988748 and lithium response. No associations between <i>NTRK2</i> SNPs and lithium response	Dmitrzak-Weglarz et al. (2008)
<i>NTRK2</i> , rs2769605, rs1387923, rs1565445	BD patients, Han Chinese (127, 157F).	rs2769605 SNP was associated with lithium response. G/G carriers manifested worse response to lithium.	Wang et al. (2013)

Table 3

Human pharmacogenetic studies related to neurotransmitter systems and lithium therapy response. BD, bipolar disorder; SNP, single nucleotide polymorphism.

Gene and marker	Subjects	Finding	Reference
<i>DRD3</i> , <i>BalI</i>	BD/major depression patients mixed, European (21M, 34F)	No association with lithium response	Serretti et al. (1998)
<i>DRD2</i> , S311C VNTR; <i>DRD4</i> multiple variants; <i>GABRA1</i> multiple variants	BD and major depression patients mixed, European (47M, 78F)	No association with lithium response	Serretti et al. (1999a)
<i>TPH</i> , <i>Bfal</i>	BD and major depression patients mixed, European (39M, 69F)	A trend toward worse lithium response was found in <i>TPH</i> *A/A variant carriers.	Serretti et al. (1999b)
<i>HTR2A</i> T102C, C1420T; <i>HTR2C</i> Cys23-Ser23; <i>HTR1A</i> no variant was found	BD and major depression patients mixed, European (49M, 75F with different subject numbers for each gene)	No association with lithium response	Serretti et al. (2000)
<i>5-HTTLPR</i> (a 44-bp promoter polymorphism that regulates expression levels)	BD/major depression patients mixed, European (83M, 118F)	Homozygous carriers of the short variant were associated with a worse response to lithium.	Serretti et al. (2001)
<i>COMT</i> , G158A; <i>MAOA</i> -30 bp uVNTR; <i>GNB3</i> C825T	BD/major depression patients mixed, European (N = 201, with different subject numbers for each gene)	No association with lithium response	Serretti et al. (2002)
<i>5-HTTLPR</i>	BD patients, European (28M, 55F)	Homozygous carriers of the long variant were associated with a worse response to lithium.	Serretti et al. (2004)
<i>HTR2A</i> , T102C; <i>HTR2C</i> , G68C	BD patients, European (39M, 53F)	No association with lithium response	Dmitrzak-Węglarz et al. (2005)
<i>5-HTTLPR</i>	BD patients, European (27M, 40F)	Short allele carriers were associated with a worse response to lithium.	Rybakowski et al. (2005b)
<i>5-HTTLPR</i> ; <i>TFAP2B</i> , CAAA	BD patients, mixed backgrounds, mostly Caucasian (43M, 91F)	No association with lithium response	Michelon et al. (2006)
<i>CACNG2</i> , rs2284017, rs2284018, rs5750285 (and nine additional SNPs)	BD patients and controls from two different European centers (N = 383)	rs2284017, rs2284018 and rs5750285 were found to be associated with lithium response.	Silberberg et al. (2008)
<i>5-HTTLPR</i>	Treatment resistant depression patients, European (22M, 28F)	Homozygous carriers of the short variant were associated with response to lithium augmentation.	Stamm et al. (2008)
<i>HTR2A</i> , <i>MspI</i> ; <i>DRD1</i> , T800C, A48G, T1403C; <i>DRD2</i> , <i>NcoI</i> , TaqIA; <i>DRD3</i> , <i>MscI</i> ; <i>DAT1</i> , VNTR; <i>5-HTTLPR</i>	BD/schizoaffective disorder BD type patients, European (42M, 113F)	No association with lithium response	Manchia et al. (2009a)
Genome-wide association study	BD patients, multiple centers (N = 458 in US, N = 359 in UK)	No SNPs reached genome-wide significance. Suggestive evidence for association with lithium response from SNPs including the chromosomal region of <i>GRIA2</i> gene among others	Perlis et al. (2009)
<i>DRD1</i> , -48 A/G	BD patients, European (39M, 53F)	G/G genotype significantly less likely to be found in excellent responders	Rybakowski et al. (2009)
<i>FYN</i> , rs706895, rs6916861, rs3730353	BD patients, European (43M, 58F)	A trend was observed toward an association between the T allele of rs3730353 and worse lithium response.	Szczepankiewicz et al. (2009a)
<i>GRIN2B</i> , rs7301328, rs890, rs1019385	BD patients, European (42M, 63F)	No association with lithium response.	Szczepankiewicz et al. (2009b)

Gene and marker	Subjects	Finding	Reference
<i>5-HTTLPR</i> , STin2 VNTR	BD patients (65M, 57F)	STin2.12/10 and 10/10 variants when combined together were associated a worse response to lithium. <i>5-HTTLPR</i> variants were not associated with lithium response.	Tharoor et al. (2013)
Genome-wide association study	BD patients, Han Chinese (191M, 203F)	Significant genome-wide associations between lithium response and intronic SNPs rs17026688 and rs17026651 ($P = 1.66 \times 10^{-49}$ and $P = 7.07 \times 10^{-50}$), located within the <i>GADL1</i> gene.	Chen et al. (2014)

Table 4

Human pharmacogenetic studies of circadian system related genes and lithium therapy response. BD, bipolar disorder; SNP, single nucleotide polymorphism.

Gene and marker	Subjects	Finding	Reference
<i>NR1D1</i> , rs4794826, rs2314339, rs2071427, rs2269457, rs12941497, rs939347, rs2071570	BD patients, European (N = 170)	T allele carriers of rs2314339 SNP were associated with a worse response to lithium.	Campos-de-Sousa et al. (2010)
<i>NR1D1</i> , rs12941497, rs939347	BD patients, European (59M, 140F)	No association with lithium response	Manchia et al. (2009b)
<i>ARTNL</i> , rs2279287, rs1982350, rs2278749; <i>CLOCK</i> , rs1801260, rs3736544, rs34897046; <i>PER2</i> , rs2304672; <i>PER3</i> , rs228729, rs228642, rs228666, rs228697, rs2859388, rs2640909	BD patients, Caucasian (N = 282)	No association with lithium response	McCarthy et al. (2011)
<i>CRY1</i> , rs8192440; <i>NR1D1</i> , rs2071427	BD patients, Caucasian (N = 282)	Nominal associations between both SNPs and lithium response	McCarthy et al. (2011)