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Clinical, Biological and Genetic Predictors of Lithium Treatment Response

Lityuma Tedavi Yanıtının Klinik, Biyolojik ve Genetik Yordayıcıları

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Öz

Lityum, 1800'lü yılların başında İsveçli Arfvedson tarafından keşfedilmiş ve 1950'li yıllarda psikiyatri alanında kullanılmaya başlanmıştır. Yetişkinlerde bipolar tedavisinde ilk sırada gelen bir duygudurum düzenleyici ve altın standart bir tedavi ajanıdır. Ancak, klinik uygulamada bireyler arasında lityum tedavisine yanıt oranları hastaların farklı özellikleri nedeniyle oldukça değişken olup, hangi hastanın lityuma iyi yanıt vereceğini öngörmek çoğunlukla zordur. Lityum tedavi yanıtını öngörmede klinisyenler öncelikle klinik bir fenotipi tanımaya odaklanmış gibi durmaktadır. Bu yazıda lityum tedavi yanıtının yordayıcıları ile ilgili araştırmalar gözden geçirilerek; klinik, biyokimyasal, nörogörüntüleme ve genetik yordayıcılar olmak üzere dört başlık altında ele alınmıştır.
Anahtar sözcükler: Lityum, bipolar bozukluk, tedavi, yordayıcılar.

Abstract

Lithium was discovered by the Swedish Arfvedson at the beginning of the 1800s and began to be used in psychiatry for the past 1950s. Lithium, as a mood stabilizer, is the gold standard and first choice treatment agent for the treatment of bipolar disorders in adults. However, it is mostly difficult in clinical practice to predict which patient would respond to the treatment with lithium well due to the huge variation in patients' characteristics. Clinicians seem to focus primarily on identifying a clinical phenotype to foresee lithium treatment response. In this article, researches on predictors of the lithium treatment response were reviewed and evaluated in four titles as clinical, biochemical, neuroimaging and genetic predictors.
Key words*:* Lithium, bipolar disorder, treatment, predictors.

BİPOLAR DISORDER (BD) is a common chronic disease that is characterized by recurrent mood episodes. Approximately 80% of patients with BD have a new mood episode within the first two years after an initial mood episode (Goodwin and Jamison 2007, NICE 2014). BD also has higher rate of other medical comorbidities and higher risk of suicide. There is a 6-10 fold increase in premature death compared to the general population (Hayes et al. 2015). Not surprisingly, BD is among the most severe 10 diseases all around the world (Lopez and Murray 1998, Collins et al. 2011). Lithium which has been used in the treatment of the disease for long years was discovered by the

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Swedish Arfvedson at the beginning of the 1800s and then was used in the treatment of some kidney diseases. It was first noticed in 1886 that it was effective in psychiatric diseases, especially in acute and preventive treatment of depression. Although its first use in psychiatry field began in the 1950s, its actual use extends back to the 1970s. In 1949, John Cade noticed that lithium urate caused lethargy at high doses in experimental animals, and then determined that lithium carbonate was an effective antimanic agent (Schou 2001). In the later years, its use has increasingly become common due to the regulatory effects of lithium on mood.

Lithium has been reported to reduce relapse, suicide, and premature mortality as well as to improve cognitive functions in the preventive treatment of BD when compared to lack of treatment or inadequate treatment (Sportiche et al. 2017). Considering the significant positive effects of lithium on morbidity and mortality in treatment for BD, lithium is considered as the gold standard therapy in clinical practices and significantly reduces recurrence rates when compared to placebo or other anticonvulsant mood stabilizers regardless of polarity (Geddes et al. 2004, BALANCE Investigators and Collaborators et al. 2010, Severus et al. 2014). Lithium is the primary treatment option for the prevention of recurrent mood episodes in bipolar disorder among adults (Grof and Muller-Oerlinghausen 2009, Yatham et al. 2013). Moreover, it is the only mood stabilizer known to have anti-suicide effects in patients with bipolar disorder (Muller-Oerlinghausen et al. 1992, Goodwin et al. 2003, Cipriani et al. 2005, Baldessarini and Tondo 2008). When lithium treatment is started particularly in the early period, the rate of response to lithium treatment may be higher (Kessing et al. 2014) and the neuroprotective effects of lithium may be greater (Hajek et al. 2013, Pfennig et al. 2014, Malhi and Outhred 2016). Although its effectiveness is well known in adults, the efficacy, tolerability, and acceptability of lithium treatment have been relatively less studied in children and adolescents. As a result, most of guidelines and studies seem to focus on adult patients (Yatham et al. 2013, Fountoulakis et al. 2016).

Lithium is the first drug to be released into the market as a mood stabilizer. Since it has been used for many years, many studies have been conducted on it. Because its efficacy and side effect profile has been well defined, it is recommended as a first-line drug for preventive treatment in treatment guidelines (Tondo et al. 2001). We still have limited information about its therapeutic mechanism although it has been commonly used in the treatment of BD for longer than a half century (Malhi and Outhred 2016). Although its mechanism of action is still unclear, it is thought that lithium regulates G proteins in the phosphatidylinositol system via the second messenger system, inhibits inositol monophosphatase, and has regulatory effects on gene expression for growth factors and neuronal plasticity by inhibiting protein kinase C and glycogen synthase kinase-3 (Ünal et al. 2013). In particular, recent studies have emphasized that lithium makes changes on the cell membrane and nucleus, second messenger molecules, and neurotransmitter systems. However, the mechanism of its positive effects on depressive and manic episodes has not yet been understood precisely (Jefferson and Greist 2000). For this reason, it has not been possible to determine which patient will respond better or worse during which episode. Therefore, the fact that the biologic predictors of lithium treatment response can be more clearly identified can help to predict which patient will respond better to lithium treatment or which patient will experience side effects related to lithium treatment. Thus, it may also increase confidence for lithium prescri-

bing (Schulze et al. 2010).

The first information on lithium treatment response were obtained from personal clinical experiences and observational studies. Clinicians seem to focus primarily on identifying a clinical phenotype (Schulze et al. 2010). In this article, after studies on the predictors of lithium treatment response were reviewed, it was evaluated under four headings as clinical, biochemical, neuroimaging, and genetic predictors.

Table 1. The biochemical predictors which are investigated to assess the lithium response

Study	Methods	Results
Mendels and Frazer 1973	BD (n=9) MDD (n=4), prospective study	Better responses in the ones with higher RBC/plasma lithium rate
Shapiro et al. 1976	BD (n=47)	A positive relation between HLA-A3, HLA-B7 and HLA-Bw16 and BD; A negative relation between HLA-B8 and BD
Perris et al. 1979	Psychotic BD (n=33) Psychotic Unipolar Recurrent Depression (n=29) Cycloid Psycosis (n=20)	HLA-A3 antigene frequency more in the ones not responding to lithium
Campbell et al. 1984	BD (n=37)	Unrelated mood disorder with HLA
Kato et al. 1993	BD (n=8)	In predicting response, the brain lithium concentration; more correlated serum and RBC concentration
Kato et al. 1994	BD in manic period (n=14)	More related responses to lithium with the brain lithium concentration in manic period
Kusumi et al. 2000	BD (n=24) Melancholic MDD (n=51) Non-melancholic MDD (n=23), prospective study	Good responses to the lithium treatment but bad responses to antidepressants of depressed patients with higher calcium response induced by serotonin
Gülöksüz et al. (2012)	Euthymia BD (n=60)	Significantly higher TNF-a levels in the ones responding to lithium badly
Debnath et al. 2013	BD (n=516) Control Group (n=161)	Lower HLA-G 14 base pair insertion/insertion genotype in BD patients than healthy controls

BB, bipolar disorder; MDD, major depressive disorder; HLA, human leucocyte antigen; IMPase, inositol phosphatase; TNF-a, tumor necrosis factor

Clinical Predictors

The efficacy of prophylactic treatment against recurrence of manic and depressive episodes during long-term lithium treatment can be assessed with retrospective and prospective studies. Treatment responses are divided into three categories: (1) full responders (no mood episodes during lithium treatment); (2) partial responders (50% reduction in the number of mood episodes when compared to prelithium period); (3) non-responders/poor responders (less than 50% reduction in the number of mood episodes, no change or worsening when compared to prelithium period) (Sportiche et al. 2017).

Today, one of the scales that measure the response to preventive treatment is the 'Preventative Treatment Assessment Scale' (the Alda scale) developed by Grof et al.

(2002) (Rybakowski et al. 2014). This scale is a measure that assesses the healing effect of preventive treatment on the course of disease by taking into account clinical factors. In this scale, criterion A rates the degree of response (activity of the illness while on adequate lithium treatment) on a 10-point scale. Criteria B1-B5 establish whether there is a causal relationship between the improvement and the treatment. Criterion B involves B1: the number of episodes before the treatment, B2: frequency of episode before the treatment, B3: the duration of treatment, B4: compliance during period(s) of stability, and B5: the use of additional medications during the periods of stability. Higher scores of the 'Alda scale' indicate a good response to lithium. The total score (TS) ranges from 0 to 10 and is obtained by subtracting score B from score A. Patients with TS ≥7 are defined as full responders, while patients with TS ≤6 are partial or nonresponders. This scale has been used in many studies evaluated in our article.

Although lithium is known to be a highly effective treatment for BB according to studies, the rate of response to lithium treatment among individuals varies considerably in clinical practice. Rybakowski et al. (2001) reported that approximately 30% of individuals treated with lithium responded perfectly; for instance, there was no any mood episode during a 10-year lithium preventative treatment. Grof et al. (2002) indicated that the response rate in first-degree relatives of these individuals may increase further. Furthermore, it was reported that approximately 30% of patients with BD responded partially to lithium treatment in clinical practice and that nearly 40% of them were nonresponsive to treatment (Baldessarini and Tondo 2000, Garnham et al. 2007). Considering these findings, the response to lithium treatment is predicted by determining the personal and clinical characteristics of individuals with and without recurrence during prophylactic treatment with lithium.

Studies conducted to identify clinically relevant indicators for good lithium response have revealed conflicting results. Two well-known clinical indicators of ideal response include the history of good response to lithium in the first degree relatives and the presence of remissions between mood episodes (Grof et al. 2002). Some clinical characteristics such as bipolar subtype, number of mood episodes before initiation of lithium, age at onset of illness, type of first episode, rapid cycling, psychiatric and other medical comorbidities, and atypical depression are other clinical predictors of treatment response (Sportiche et al. 2017).

In a systematic review evaluating 43 studies and 42 clinical variables, Kleindienst et al. (2005) have indicated that there are only five potential predictors of clinical response to lithium treatment. Among clinical factors, the strongest predictors of good response are fewer hospitalizations preceding treatment, an episodic course characterized by an illness pattern of mania followed by depression (MDI), and a later age at onset of bipolar disorder. The strongest predictors of poor response are more hospitalizations preceding treatment, rapid cycling, and an episodic course characterized by an illness pattern of depression followed by mania (DMI). However, different results were obtained in later studies. For instance, Garnham et al. (2007) reported that early age at onset of illness, presence of periodic mood episodes (regardless of MDI or DMI), and meeting the diagnostic criteria for bipolar I disorder were associated with better response. Pfennig et al. (2010) found that the likelihood of recurrence in patients treated with lithium was positively related to mood-incongruent psychotic symptoms, residual symptoms, and rapid cycling. Kessing et al. (2011) indicated that good lithium response was rela-

ted to fewer hospitalizations in psychiatric clinics, mania-dominant polarity, and fewer somatic comorbidities.

In a current independent study of Sportiche et al. (2017), they investigated three response groups (full response, partial response, unresponsiveness) characterized using the 'lithium treatment response scale' in 300 patients with bipolar disorder receiving lithium treatment for at least 6 months. In this study, only three clinical factors from the previously mentioned predictors for good lithium response showed significant differences between the three pre-defined response groups. From among these, the positive family history of bipolar I disorder was found to be associated with a good response whereas the presence of mixed episodes and the history of alcohol use disorders were found to be associated with a poor response. Another noteworthy condition is that the positive family history of bipolar I disorder is a facilitating factor for improvement, while the positive family history of bipolar II disorder has a tendency in the opposite direction. In this study, there was no statistically significant relationship with age at onset of illness, duration of illness before initiation of lithium, clinical features (bipolar subtype, onset polarity, seasonality, rapid cycle, psychotic findings, suicide attempts) or other psychiatric comorbidities (anxiety disorder or substance abuse).

Biochemical Predictors

Some chemical factors can be used in showing the efficiency of lithium and in predicting lithium response (as summarized at Table 1). Some of these have been reported and accepted in their articles by different authors (Rohayem et al. 2008). For instance, it was reported that higher levels of lithium in red blood cells (RBC) compared to serum were associated with better response to lithium treatment. Firstly, Mendels and Frazer (1973) revealed that depressed patients who responded to lithium treatment had higher RBC/plasma lithium ratios than nonresponders. However, they then reported that they could not achieve the same result in a larger sample (Frazer et al. 1978). With using lithium-7 magnetic resonance spectroscopy (7Li-MRS), which allows the measurement of lithium levels in the brain, in studies in parallel with technological improvements (Renshaw and Wicklund 1988, Komoroski et al. 1990, Kato et al. 1992, Sachs et al. 1995), it has been found that brain lithium concentrations are more correlated with serum lithium concentrations than erythrocyte lithium concentrations (Kato et al. 1993). As a result, given the possible relationship between the RBC lithium concentration and the positive lithium response, it is not wrong to say that the RBC lithium concentration is a good parameter for reflecting the brain lithium concentration. Similarly, a study using 7Li-MRS has also detected that, in manic patients, a brain lithium concentration of ≥0.2mEq/L, which approximately corresponds to a serum concentration of ≥0.4mEq/L, is a more useful predictor of lithium response than serum concentration (Kato et al. 1994). These studies support the hypothesis that brain lithium levels are a better predictor than plasma lithium levels (Ikeda and Kato 2003). In contrast, with regard to lithium prophylaxis, correlation between brain concentration and clinical effectiveness was not supported (Kato et al. 1994).

Another reported biochemical predictor is the human leukocyte antigen (HLA) present on the cell membrane surface. There is some evidence that there is an association between particular HLA types and some specific diseases (Ryder et al. 1974). In psychiatry, HLA frequencies in schizophrenic patients were first studied (Cazzullo et

al. 1974), and then an association between HLA typing and BD was also reported (Ventura et al. 1990, Debnath et al. 2013). It was found that BD had a positive association with HLA-A3, HLA-B7, HLA-B16 and a negative association with HLA-B8 (Shapiro et al. 1976, Shapiro et al. 1977). However, Beckman et al. (1978) claimed a decreased frequency of the B7 antigen in patients with affective disorders. Perris et al. (1979) found that the frequency of HLA - A3 antigen was significantly higher in lithium non - responders. This relationship between HLA - A3 antigen and non - response to prophylactic treatment by lithium was confirmed by other researchers (Del Vecchio et al. 1981, Maj et al. 1984, Maj et al. 1985). However, subsequent studies could not replicate an association between affective disorder and HLA antigens (Targum et al. 1979, Johnson et al. 1981, Goldin et al. 1982, Campbell et al. 1984).

A possible relationship between intracellular calcium signaling systems and BD has been reported since the early 1980s (Dubovski and Franks 1983, Yamawaki et al. 1998). Lithium has been reported to affect intracellular calcium signaling mainly by inhibiting inositol monophosphatase (IMPase) (Meltzer 1986, Berridge 1989). It is thought either spontaneous inhibition of IMPase or subsequent downregulation of IMPase gene expression may be related to clinical efficacy of lithium in the treatment of bipolar disorder (Atack et al. 1995, Shaldubina et al. 2001). For this reason, interindividual variation of these parameters may become a good predictor of lithium response. On the other hand, higher intracellular calcium concentrations (Emamghoreishi and Schlichter 1997) and and lower expression levels of IMPase mRNA (Nemanov et al. 1999) have been reported in transformed lymphoblastoid cell lines derived from patients with bipolar disorder. Yoon et al. (2001) examined the relationship between intracellular calcium concentration and IMPase mRNA expression in patients with bipolar I disorder and found a significant negative correlation between IMPase2 mRNA levels and calcium concentrations in the cell lines from male patients with bipolar I disorder.

Similarly, Kusumi et al. have investigated serotonin - induced platelet intracellular calcium mobilization (Kusumi et al. 1994, Kusumi et al. 2000, Suzuki et al. 2001). They have suggested that serotonin - induced platelet intracellular calcium mobilization is specific to bipolar disorder. Initially, they reported that the elevated serotonin - induced calcium response was significantly higher not only in unmedicated patients with bipolar depression, but also in patients with melancholic major depression (Kusumi et al. 1994). They also found that depressed patients with a higher serotonin - induced calcium response exhibited a good response to lithium treatment but had a poor response to antidepressants (Kusumi et al. 2000). However, it was reported that there were no significant differences in basal intracellular calcium concentration among patient groups and normal controls.

In recent times, the role of inflammation in BD has emerged as a promising mechanism. With the identification of effects of cytokines on neuromodulation, many studies have begun to focus on the role of cytokines in mood disorders. Tumor necrosis factor-alpha (TNF-a), a proinflammatory cytokine, is one of these cytokines. Gülöksüz et al. (2012) measured plasma TNF-a levels in 60 euthymic patients with BD receiving lithium treatment and assessed the patients' responses to lithium treatment as good, partial, and poor by using the Alda scale. As a result, they reported that patients who responded poorly to lithium had significantly higher plasma TNF-a levels when compared to patients who responded well to lithium.

In summary, studies suggest that there may be a relationship between intracellular calcium signal and lithium response in BD. In particular, lower IMPase mRNA levels and higher serotonin - induced calcium mobilization become prominent as biological predictors of lithium response. However, whether or not basal intracellular calcium concentration may be a good predictor of lithium response is still controversial. Most of the possible biological predictors of better lithium response in bipolar disorder (such as lower IMPase mRNA levels, white matter hyperintensity, lower brain intracellular pH, enhanced calcium response, and PLCG1 - 5 repeat) have been shown to be risk factors for bipolar disorder (Swayze et al. 1990, Altshuler et al. 1995, Kato et al. 1998, Suzuki et al. 2001). As a result of these studies, several findings have been obtained that bipolar disorder responding well to lithium therapy has a certain neurobiological basis. However, further evidence is needed to confirm these findings. The neurobiological basis of resistance to lithium treatment is still controversial.

Neuroimaging Predictors

Bipolar Disorder (BD) appears to be associated with neuroanatomical, neurochemical, and functional abnormalities in neuroanatomical circuits modulating mood. The information obtained by brain imaging methods allows for the investigation of underlying brain mechanisms of BD as well as therapeutic effect of lithium. Brain imaging studies have reported that lithium makes different functional and neurochemical changes in the brain in patients with BD (Silverstone et al. 2003). Lithium treatment was found to be associated with increased gray matter volume in brain regions such as the hippocampus (Yücel et al. 2007, Foland et al. 2008) and the amygdala (Foland et al. 2008, Usher et al. 2010, Moore et al. 2000).

Magnetic resonance spectroscopy (MRS) studies have reported increased amygdala and hippocampal volumes in bipolar patients with lithium treatment. Some studies have suggested that the increase in brain volume occurs due to the osmotic effects of lithium and its effects on signal changes in imaging techniques. Cousins et al. (2013) have suggested that lithium can directly affect magnetic resonance imaging signal intensity with the contribution of its biological effects as well as its atomic-level effects. For this reason, they have reported that volumetric findings can be artifacts due to altered image contrast caused by lithium. Although the underlying factors of gray matter changes associated with lithium are still unclear, it is suggested that these changes may be due to the fact that lithium shortens the T1 relaxation time on MRI (Cousins et al. 2013). However, it is very difficult to explain lithium-related regional brain volume changes without global brain volume changes with shortening of T1 relaxation time by lithium (Vernon and Hajek 2013). Lyoo et al. (2010) have reported that gray matter volume changes occur due to the neurotrophic effects of lithium rather than the osmotic effects of lithium. On the other hand, the relationship between cortical thickness and increased levels of N-acetyl-aspartate with lithium treatment suggests that lithium increases synaptic density and is neuroprotective (Curran and Ravindran 2014).

Although the molecular mechanisms underlying the therapeutic effects of lithium are not known precisely, it is suggested that lithium treatment may suppress overactive neural networks in BD through the consumption of myoinositol which is a component of the secondary messenger system (Tighe et al. 2011). Friedman et al. (2004) showed that lithium treatment changed cerebral myoinositol (MI) levels in their MRS study.

Davanzo et al. (2001) compared MI levels of 11 bipolar children treated with lithium with 11 basic screenings from gender- and age-appropriate controls using proton MRS and 11 children with BD treated with lithium. They reported that the patients responding to lithium had significant reduction in anterior cingulate MI compared to pretreatment levels after 1 week of treatment. Despite these studies, the obtained findings do not support that lithium-induced changes in the phosphatidylinositol cycle occur through the mechanism of clinical response to lithium (Silverstone and McGrath 2013).

As another predictor, choline (Cho) is an important component of the plasma membrane and plays an important role in membrane functions. The choline peak on MRS contains a variety of choline molecules, including a small fraction of free choline. It was reported that there was increased choline peak in the basal ganglia of patients with BD (Soares et al. 1996). The Cho concentrations showed few differences between gray and white matter. However, since the creatine-phosphocreatine (Cr-PCr) ratio is higher in gray matter, a larger percentage of gray matter corresponds with a lower Cho/Cr-PCr ratio (Noworolski et al. 1999). Moore et al. (2000) found an increase in the Cho/PCr-Cr ratio in the right anterior cingulate gyrus of bipolar patients. The increase in choline-containing molecules in the basal ganglia reported in many studies seems to be irrespective of lithium treatment and may represent an important aspect of the pathophysiology of these disorders.

Kato et al. (2000a) suggested that white matter hyperintensity can be a positive predictor of lithium response in a limited number of patients examined by MRI. It is generally reported that patients with neurological signs and lesions may be better able to respond to anticonvulsants than to lithium. This finding does not seem to be consistent with the literature in this respect. Kato et al. (2000b) found that decreased intracellular pH was significantly associated with positive lithium response and that increased phosphodiester (PDE) and decreased phosphocreatine tended to be associated with poor lithium response. They indicated that these findings were consistent with P-MRS findings (such as that lower intracellular pH values responded well to lithium and higher PDE values and lower PCr values responded poorly to lithium) previously reported in BD. Murashita et al. (2000) investigated brain energy metabolism in lithium - resistant bipolar disorder using the photic - stimulation paradigm in ^{31}P - MRS. The phosphocreatine peak area ratio was significantly decreased after photic - stimulation in lithium - resistant bipolar patients. For this reason, decreased phosphocreatine may be worth studying as a negative predictor of lithium response. It is possible that mitochondrial function is impaired in lithium - resistant bipolar disorder (İkeda and Kato 2003).

Fleck et al. (2017) investigated the predictability of lithium response using fMRI and Proton MRS as well as a machine learning system in a system called LITHIA in the first episode of mania. They have shown that this system can determine lithium response with an accuracy rate of 88% and a validity rate of 80%. Despite small sample size of this study, short follow-up duration of patients, heterogeneous nature of the brain, limited standardization available in imaging methods, and restrictions in machine learning techniques, further studies in the field of similar machine learning systems may be promising in predicting lithium response.

Lithium has significant effects on Electro Encephalogram (EEG). There is no doubt that EEG will give information about lithium-induced biochemical and biophysical

features in the brain (Atagün et al. 2015). Tan et al. (2016) found that beta oscillations in response to a visual target stimulus were significantly higher in euthymic bipolar patients receiving lithium compared to bipolar patients not receiving lithium and healthy controls. They argued that increased beta oscillations in bipolar patients receiving lithium may be a reflection of the negative effects of lithium on cognitive functions, rather than the therapeutic effects of lithium. Atagün et al. (2015) examined brain oscillatory responses using a auditory oddball paradigm. They found that lithium increased auditory-related beta amplitudes in response to a target stimulus. They suggested that their findings were consistent with previous studies reporting increased white matter connectivity, increased gray matter volume, increased brain lithium concentration or improved brain biochemistry. When considering the relevant studies, lithium-EEG studies may be considered to considered to have more informative intermediate phenotypic characteristics than many other methods including magnetic resonance imaging techniques. None of these findings have yet been shown in subsequent studies. Therefore, further studies are needed to characterize lithium response in bipolar patients by neuroimaging.

Genetic Predictors

Clustering of both BD and lithium response in families suggests the importance of genetics in disease occurrence and treatment response (Groff et al. 2002). The disease itself appears to be the most heritable disease among all psychiatric disorders, and the predictors of lithium response seem to be a relatively homogeneous subtype of BD (Alda et al. 2006). Twin studies reported that monozygotic and dizygotic twin pairs gave similar responses to lithium (Mendlewicz et al. 1979). Mendlewicz et al. (1978) investigated lithium distribution in red blood cells with 42 twin pairs with BD. They determined that concordant bipolar twin pairs had a better response to lithium than discordant pairs. Only 30% of patients with good treatment adherence are fully responsive to lithium treatment, and there is considerable evidence that there are patients groups with partial or inadequate response to lithium treatment (Baldessarini 2000, Rybakowski 2001, Manchia 2013). The difficulty in predicting lithium response through clinical variables and the recent developments in molecular genetic technology encourage investigation of the genetic predictors of lithium response (as summarised at Table 2) (Kleindienst et al. 2005a).

The serotonin transporter gene (5-HTTLPR) produces a protein that plays a role in the reuptake of serotonin in the synaptic cleft. It has a 44 bp insertion/deletion polymorphism within the promoter region (5-HTTLPR) with two allelic forms, the long (L) and the short (S) variants. Serretti et al. (2001) prospectively examined lithium response over 4 years in 201 patients (167 bipolar patients and 34 major depression patients). They revealed that patients with the s/s variant had a worse response compared to patients with the l/s or l/l variants.

Rybakowski et al. (2005a) found that the frequency of 's' allele was significantly higher in lithium non-responders than in partial/good lithium responders among 67 patients with BD ($p = 0.05$). Contrary to these results, Del Zompo et al. (1999) informed that the frequency of l/l allele was significantly higher in poor lithium responders from among 67 Italian patients with BD.

Table 2. The genes which are investigaed to assess the lithium response and the results

Study	Method	Results
Serretti et al. 1998	BD (n=43) MDD (n=12)	Unrelated D3 gene variants of dopamin receptor with the lithium response
Steen et al. 1998	a) BD (n=23), control (n=20) b) BD (n=54), control (n=50)	Polymorphisms in the coding area of INPP1 gene; a) More C973A allel of INPP1 gene in the ones responding to lithium b) Unrelated with the lithium response
Turecki et al. 1998	BD (n=136), control (n=163)	In the ones giving good responses to lithium, unrelated gene encoding PLCG1 isoenzyme
Serretti et al. 1999a	BD (n=100), MDD (n=25)	Unrelated the DRD2, DRD4,GABRA1 gene variants with the lithium response
Serreti et al. 1999b	BD (n=90), MDD (n=18)	Poorly related tryptophane hydroxylase (TPH) gene variants with the lithium response
Del zompo et al. 1999	BD (n=67), retrospective study	Higher l/l allel frequency in the ones giving bad responses to lithium
Ewald et al. 1999	BD (n=18), haplotype based genetical study	Related 18q23 chromosomal area with the lithium response
Serreti et al. 2001	BD (n=167), MDD (n=34)	5-HTTLPR gene variants; Worse response from s / s genotype s / l and l / l', but for bipolar diseases ineffective by oneself
Løvlie et al. 2001	BD (n=61), control (n=50)	In patients with BB diagnosis, unrelated with PLCG1-5 and PLCG1-8 alleles
Turecki et al. 2001	BD (n=31), genom screening	The patients responding to lithium well linked with locus on chromosome 15q14 and 7q11.2
Washizuka et al. 2003	BD (n=54)	MtDNA 5178 and 10398 polymorphisms; MtDNA 5178 genotype ineffective, but a significant relation between the 10398A polymorphism and the lithium response
Rybakowski et al. 2005a	BD (n=67)	5-HTTLPR s and l alleles; significantly more often s/s genotype and s allel in the ones giving less response
Rybakowski 2005b	BD (n=88)	More often in the ones giving good responses on Val / Met genotype of BDNF from Val66Met and -270C/T polymorphisms of BDNF gene
Masui et al. 2006	BD (n=66)	XBP1 -116C/G polymorphism; More effective lithium, -116C allel transporter, -116G homozygotes
Rybakowski et al. 2007	BD (n=111)	Significantly more often in the individuals not responding to lithium from 5-HTTLPR s and l alleles and BDNF Val66Met genotypes.
Ferreira et al. 2008	Olgu (n=4387), control (n=6209)	No strong relation between the ANK3 and the the lithium response
Baum et al. 2008	GWAS	No strong relation between the BD and the DGK gene
Mamdani et al. 2008	BD (n=249), control (n=127)	Unrelated CREB1 gene polymorphisms with the

		lithium response
Silberberg et al. 2008	BD (n=35) Schizophrenia (n=35) Control (n=35), genotype	About the CACNG2 gene, three related SNPs with the lithium response (rs2284017, rs2284018, rs5750285)
Perlis et al. 2009	BD (n=458), GWAS	Related chromosome areas 8q22, 3p22, 11q14, 4q32 and 15q26 with the lithium response
Squassina et al. 2011	BD (n=204), GWAS	Related ACCN1 with the lithium response
Shulze et al. 2012	ConLİGen	Unrelated SCL4A10 with the lithium response
Chen et al. 2014	BD (n=294), GWAS	A significant relation in the GADL1 gene localization
Tobe et al. 2017		Pluripotent stem cells; Increased phosphorylation of CRMP2 in the patients responding to lithium
Mitjans et al. 2015		GSK-3β polymorphisms; A significant relation between the rs1732170, rs11921360 and rs334558 polymorphisms and responses to the lithium treatment
Altınbaş et al. 2017	BD (n=100)	GSK-3β polymorphisms; higher points of responses to the lithium treatment in the patients with rs17183890 AG genotype

BD, bipolar disorder; GWAS, genom-wide association study; MDD, major depressive disorder; SNP, Single nucleotide polymorphism

Brain-derived neurotrophic factor (BDNF) is another genetic predictor. It affects neuronal proliferation and synaptic plastisity. BDNF has also been found to be associated with the mechanisms of action of antidepressants and lithium (Green et al. 2006). The Val66Met (Val66Met or G196A) polymorphism of the BDNF gene has been related to the occurrence of BD (Sklar et al. 2002, Green et al. 2006). Although two retrospective studies did not prove the relationship between the BDNF val66Met genotype and the lithium response in bipolar patients (Masui et al. 2006, Michelon et al. 2006), several subsequent studies reported that the val/met genotype appeared to be more common in those who responded well to lithium than in those who did not respond to lithium (Rybakowski et al. 2005b, Dmitrzak-Weglarz et al. 2008). The same researchers retrospectively examined the possible association between the serotonin transporter genotype (5-HTTLPR) and the BDNF val66Met polymorphism according to lithium response. They evaluated 111 patients with BD and reported that the 5-HTTLPR s/s or s/l genotype and the BDNF val/val genotype were significantly more common in patients who did not respond to lithium (Rybakowski et al. 2007).

One of the possible mechanisms of action of lithium is that it makes changes on the second messenger system. The INPP1 gene encodes the enzyme inositol polyphosphate-1-phosphatase (IPPaz) which dephosphorylates inositol 1,3,4-trisphosphate and inositol 1,4-bisphosphate as a part of the phospholipase C signaling system. This gene is of interest as a potential modulator of lithium response. In a retrospective study of Steen et al. (1998) involving 23 patients with BD and 20 controls, they found that a single-nucleotide polymorphism (C973A) in the INPP1 coding region indicated good lithium response. However, when this study was repeated in a larger sample of 54 patients with BD, it was reported that this polymorphism did not differ significantly

between those who responded well to lithium and those who responded poorly to lithium in terms of predicting lithium response (Steen et al. 1998). The data obtained so far suggest that this INPP1 variant is not associated with lithium response in bipolar patients. Turecki et al. (1998) investigated polymorphisms of the phospholipase C gamma 1 (PLCG1) gene in 163 healthy controls and 136 bipolar patients who responded well to lithium. They found that patients who responded well to lithium treatment had a higher frequency of the gene encoding the PLCG1 isoenzyme on chromosome 20. Similarly, Løvlie et al. (2001) retrospectively investigated polymorphisms of the PLCG1 gene in 61 patients with BD and 50 healthy controls. They found that patients with BD had a higher frequency of PLCG1-5 and PLCG1-8 alleles than healthy controls.

It is also thought that lithium inhibits inositol monophosphatase (IMPA) and reduces inositol levels (Manji H. et al. 1995). IMPA2 encodes an enzyme inhibited by lithium. Dimitrova et al. (2005) examined eight single-nucleotide polymorphisms (SNPs) associated with BD in the gene where this enzyme is found. No association was found between lithium response and any SNPs in the study involving 237 families. Diacylglycerol (DAG), another molecule involved in the inositol pathway, is degraded and reversed by diacylglycerol kinase (DGK). Two genome-wide association studies (GWAS) reported strong evidence that there is an association between the DGK gene and BD (Burton et al. 2007, Baum et al. 2008). Starting from these studies, the DGK gene was investigated in 199 Sardinian patients with BD who received lithium. There was no significant difference between those who responded well to lithium treatment and those who responded partially or poorly to lithium (Manchia et al. 2009).

One of the genes involved in the phosphatidylinositol signal pathway is prolyl endopeptidase or prolyl oligopeptidase (PREP). This gene is highly active in the brain, especially in the frontal cortex and in the limbic system. Williams et al. (1999) genetically investigated the possible mechanisms of action of lithium on amoebae and reported that lithium-resistant amoebae lacked the PREP gene. These results also include the findings showing the effects of the inositol second messenger system on BD and lithium. Mamdani et al. (2007) examined 9 SNPs on the PREP gene in 249 patients with BD and 126 healthy controls. They found that there were no genotypic differences between lithium responders, lithium non-responders, patients with BD, and healthy controls.

Another gene family that needs to be investigated is genes that encode CREB (cAMP responsive element binding protein). The cAMP signal transduction pathway is activated after the ligand binds to G protein–coupled receptors, resulting in CREB phosphorylation. Studies investigating the effects of lithium on CREB gene expression reported that lithium caused ineffective DNA binding and altered expression of cAMP-responsive genes by reducing CREB phosphorylation (Bezchlibnyk et al. 2002). Thus, genetic variation of the genes encoding CREB proteins is thought to help determine the response to lithium treatment. Mamdani et al. (2008) investigated three genomic SNPs in the CREB gene family in 249 patients with BD and 127 healthy controls. They found that CREB1 gene polymorphisms were associated with lithium response (Mamdani et al. 2008).

There are studies supporting that lithium interacts with protein kinase C (PKC), an important mediator of many intracellular responses against neurotransmitter signals.

PKC increases the activity of voltage-gated calcium channels. PKC binds to Ca+2 channels via PDLIM5 (an adaptor protein). It has been suggested that impaired intracellular calcium homeostasis plays an important role in mood control in BD. In a study investigating three SNPs in the PDLIM5 gene in 155 bipolar patients who received lithium, when PDLIM5 expression was assessed, no significant difference was found between those who responded well to lithium treatment and those who responded partially or poorly to lithium (Squassina et al. 2008). FYN, another member of the protein kinase family, plays a role in ion transport, regulation of the BDNF/TrkB signaling pathway, and phosphorylation of the NMDA receptor subunit 2B (GRIN2B). Therapeutic mechanisms and neuroprotective effects of lithium occur through glutamatergic neurotransmission via NMDA receptors. It has been reported that there may be a relationship between lithium response and BDNF (Rybakowski et al. 2005). Since FYN plays an important role in the effect of BDNF on the NMDA receptor, the three polymorphisms of the FYN gene have been investigated for differences in response to lithium treatment in patients diagnosed with BD. In a study conducted in 101 patients with BD, no relationship was found between FYN gene polymorphisms and lithium response (Szczepankiewicz et al. 2009).

Another molecule that is considered to be predictive of lithium treatment response is glycogen synthase kinase-3 beta (GSK-3β). GSK-3β inactivates glycogen synthase and plays a role in many metabolic pathways such as protein synthesis and plasticity in the brain. Phosphorylated GSK-3β has been reported to play an important role in the regulation of oxidative stress, neuroinflammation, and neurogenesis pathways and in the pathogenesis of BD (Gould et al. 2004, Can et al. 2014, Luca et al. 2016). Studies investigating the relationship between GSK-3β polymorphisms and lithium treatment response have found that there is an association between rs2199503 and rs6438552 polymorphisms and lithium treatment response (Can et al. 2014). Another study reported that there was a significant association between GSK-3β rs1732170, rs11921360 and rs334558 polymorphisms and lithium treatment response (Mitjans et al. 2015). In our country, a current study was conducted in 100 patients with bipolar I disorder to investigate the relationship between GSK-3β and lithium treatment response. Altınbaş et al. (2017) investigated the relation between the GSK-3β rs17183904, rs17183897, rs34009575, rs34002644, rs17183890 polymorphisms and the lithium treatment response using the lithium treatment response scale. They reported that the patients harbouring GSK-3β rs17183890 AG genotype had higher lithium treatment response scores.

Another genetic predictor is matrix metalloproteinases (MMPs) that are a family of zinc- and calcium-dependent collectively capable of degrading essentially all extracellular matrix components. MMPs play a role in chronic diseases such as cancer and heart disease and in neuropsychiatric disorders such as schizophrenia and BD. The MMP-9 gene polymorphism was investigated in 190 bipolar patients who received lithium treatment for at least 5 years. It was found that there was no association between the lithium treatment response and the MMP-9 gene polymorphism (Rybakowski et al. 2011).

A study of mitochondrial DNA (mtDNA) reported a possible association between the 5178C/10398A haplotype and the risk of BD (Kato et al. 2001). In a retrospective study involving 54 patients with BD, the patients with the 10398A mtDNA poly-

morphism were found to respond well to lithium treatment (Washizuka et al. 2003). On the other hand, no significant difference was found between 167 bipolar patients with serotonin 5-HT2A and 5-HT2C variants in terms of lithium response (Serretti et al. 2000). The X-box binding protein 1 (XBP1) is an important predictor of endoplasmic reticulum stress response. Masui et al. (2006) retrospectively investigated -116C/G polymorphism of this gene in patients with BD. They found that lithium responders were more likely to be carriers rather than homozygous for -116C allele (2006). Because this study was conducted only in a small group of Japanese patients, further studies are needed to determine whether there is a real association between the -116C/G polymorphism of the XBP1 gene and the lithium treatment response.

Ankyrin 3 (ANK3) has a role in the assembly of voltage-gated sodium channels (Nanavati et al. 2011). It is regulated down by lithium (McQuillin et al. 2007, Leussis et al. 2013). Despite the small effect size, it is promising that several genome-wide association studies that have highlighted ANK3 as a susceptibility gene (Ferreira et al. 2008, Muhleisen et al. 2014). Tryptophane hydroksilase (TPH) is an enzyme which limits the rate of serotonin biosynthesis. Serretti et al. (1999b) found that tryptophan hydroxylase (TPH) gene variants were less related to lithium treatment response in 90 bipolar patients and 18 depressive patients.

Unlike the above-mentioned findings, in a study involving 134 patients with BD (61 good lithium responders, 24 partial lithium responders, and 49 poor lithium responders), no significant differences were observed in the genotype or allele frequencies of good, partial and poor responders for BDNF G196A, INPP1 C973A, AP-2β (CAAA), 5HTTLPR, and GSK-3βA-1727T gene variants (Michelon et al. 2006). In a prospective study involving 43 patients with BD and 12 patients with major depressive disorder (MDD), the DRD3 genotypes were not found to be associated with the lithium response (Serretti et al. 1998). Similarly, no association was found between good lithium response and DRD1, DRD2, DRD3, DAT1, 5-HTTLPR and HTR2A genes in 155 Sardinian patients with BD (Manchia et al. 2009). Serretti et al. (1999a) did not find any relationhip between the lithium response and the DRD2, DRD4 and GABA receptor α-1 subunit (GABRA1) gene variants in 100 patients with BD and 25 patients with MDD in their prospective study. In another study, 92 patients with BD who received lithium treatment for at least five years were genotyped for the -48A/G polymorphism of the DRD1 gene. It was found that patients who responded partially or poorly to lithium were more likely to have the G/G genotype than patients who responded well to lithium treatment (Rybakowski et al. 2009). In a study of Turecki et al. (1999) investigating the association of MAO genetic polymorphisms with susceptibility to BD in 108 healthy controls and 138 patients with good response to lithium, they did not find a significant association between the MAO-A gene and the lithium response.

Candidate gene studies have not yielded reproducible results although they have focused on the genes that are considered to be involved in lithium therapy (McCarthy et al. 2010, Can et al. 2014). A few genome-wide association studies (GWAS) have been published on lithium response. Perlis et al. (2009) found that five chromosomal regions (8q22, 3p22, 11q14, 4q32, and 15q26) were associated with the lithium response in 458 patients with BD. Another GWAS was conducted in 204 patients with BD. SNP sequences were genotyped in 52 persons. ACCN1 (amiloride-sensitive cation channel

permeable for lithium) was found to be associated with the lithium response (Squassina et al. 2011). In another GWAS, Chen et al. (2004) selected 294 Asian patients with good response to lithium from among 1761 patients diagnosed with BD. They reported a significant association between the genome size and the SNP clusters in the GADL1 gene (Chen et al. 2014).

An international group examining patients treated with lithium together with a unit interested in the genetic basis of mood and anxiety disorders in the National Institute of Mental Health (NIMH) has established ConLiGen in order to create the largest study of genetic variation to date for investigating the genetics of lithium response. This sample has contained more than 1200 patients and has been described retrospectively with the Alda scale. This study showed that SLC4A10 (solute carrier family 4, sodium bicarbonate transporter, member 10) was associated with lithium response (Schulze et al. 2012). This gene is located on chromosome 2q24 and is present in higher level in the hippocampus and the cerebral cortex. This relationship is important because the bicarbonate sensitive pathway is one of the most important mechanisms for active lithium entry into cells.

When we examine genetic mapping studies in BD, pharmacogenetic strategy is becoming increasingly more prominent although it seems difficult due to the complexity and heterogeneity of genetic mechanisms. Turecki et al. (2001) performed genome-wide screening using 378 markers in the families of 31 bipolar patients with good response to lithium. They found that good lithium response may be associated with loci on chromosomes 15q14 and 7q11.2. In a haplotype-based genetic study of 18 bipolar patients and their families responding well to lithium in the Faroe Islands, the 18q23 chromosomal region was found to be associated with the lithium response (Ewald et al. 1999). Recently, it has been reported that the calcium channel γ2 subunit gene family (CACNG2, Stargazin) located in the 22q13.1 chromosomal region is associated with schizophrenia (Liu et al. 2005). This region is also associated with BD (Liang et al. 2002). Together with substantial evidence supporting that chromosome 22q13 is associated with BD, some evidence suggesting that CACNG2 is involved in shaping the synaptic response and that BD is associated with impaired neuroplasticity and cellular flexibility make CACNG2 an attractive candidate gene (Manji et al. 2000, Du et al. 2004). In order to determine the expression levels of CACNG2 in post-mortem brain specimens of schizophrenia patients, bipolar patients, and healthy controls, to analyze the genetic relationship between CACNG2 and these diseases, and to investigate the genetic relationship between CACNG2 and the lithium response, 12 SNPs involving CACNG2 were genotyped in 35 schizophrenia patients, 35 bipolar patients, and 35 healthy controls. It was determined that the expression level of CACNG2 was 1.6-fold higher in patients with BD. No relationship was found between 12 genotyped SNPs and BD. However, three of them were found to be significantly associated with the lithium response (Silberberg et al. 2008).

In a study using induced pluripotent stem cells from patients responsive and non-responsive to lithium treatment, it was focused on changes in protein and genes after lithium treatment. In this study, increased phosphorylation of collapsin response mediator protein 2 (CRMP2) in lithium-responsive patients was selected as an attractive candidate for future studies. CRMP2 regulates the cellular response to semaphorin-3A that is an extracellular signaling molecule that binds to neuropilin/plexin receptors.

This pathway, which has effects on synapse formation and function, shapes dendritic spine and axonal growth morphologies during development and adulthood. They showed that morphologies changed in in vitro conditions and postmortem brain specimens and also reported that it is an actual BD pathology and can be improved with lithium (Tobe et al. 2017). As a result, poor efficacy of genetic predictors in the prediction of lithium response and relatively low frequency of reported alleles indicate that genetic testing is far from contributing to clinical practice in most patients. With determination of new genetic predictors with greater potency in future studies, tests can be provided to predict the lithium response in clinical practice. However, it would be necessary to utilize pre-determined clinical predictors such as family history (Do et al. 2012). Genome-wide screening studies with larger sample sizes are needed to predict the lithium response

Conclusion

In order to investigate future clinical, genetic or biological predictors, it is necessary to develop consensus on the identification of the clinical response phenotype. Based on current data, it is thought that the 'lithium response' may create a clinical profile. The family history of mood disorder and good lithium response, presence of remissions between mood episodes, fewer hospitalizations in psychiatric clinics, mania-dominant polarity, and fewer somatic comorbidities have been found to be associated with good lithium response. With pharmacogenomic progress, genetic predictors make it easier to provide a genetic test panel for clinicians to optimally predict which bipolar patients can best respond to lithium treatment. It is noteworthy that patients with the 5-HTTLPR s/l or l/l genotype, BDNF val/met genotype, INPP1 gene polymorphism (C973A), gene encoding PLCG1 isoenzyme, CREB1 gene polymorphisms, GSK-3β rs17183904, rs17183897, rs34009575, rs34002644, rs17183890 polymorphisms, 10398A mtDNA polymorphism, 8q22, 3p22, 11q14, 4q32, 15q26, 15q14 ve 7q11.2 chromosomal regions, some SNP clusters in the GADL1 gene, and SLC4A10 gene polymorphisms respond well to lithium treatment.

None of the findings obtained with neuroimaging methods have yet been shown in subsequent studies. Neuroimaging methods and studies may expand these results. The effects of lithium on the brain and the predictors of lithium response can be better understood with other molecular, intracellular, neurotransmitter and genetic data. Therefore, in order to characterize the lithium response in bipolar patients, there is a need for further larger scale multicenter studies where clinical response phenotypes are well defined.

References

Alda M, Turecki GX, Jaitovich-Groisman I, de Lara CL, Duffy AC, Ruzickova M et al. (2006) Clinical and genetic heterogeneity of bipolar disorder. Bipolar Disord, 8(Suppl1):60.

Altınbaş K, Yeşilbaş D, İnce B, Cansız A, Sılan F, Gülöksüz S (2018) İki uçlu bozukluk hastalarında lityuma yanıt ile GSK-3β polimorfizmi ilişkisinin değerlendirilmesi. Turk Psikiyatri Derg; doi: 10.5080/u20582.

Altshuler LL, Curran JG, Hauser P, Mintz J, Denicoff K, Post R (1995) T2 hyperintensities in bipolar disorder: magnetic resonance imaging comparison and literature meta-analysis. Am J Psychiatry, 152:1139-1144.

Atack JR, Broughton HB, Pollack SJ (1995)Inositol monophosphatase—a putative target for Li+ in the treatment of bipolar disorder. Trends Neurosci, 18:343-349.

Atagün Mİ, Güntekin B, Tan D, Tülay EE, Başar E (2015) Lithium excessively enhances event related beta oscillations in patients with bipolar disorder. J Affect Disord, 170:59-65.

Balance Investigators and Collaborators, Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A et al. (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): A randomised open-label trial. Lancet 375:385–395.

Baldessarini RJ, Tondo L (2000) Does lithium treatment still work?: evidence of stable responses over three decades. Arch Gen Psychiatry, 57:187-190.

Baldessarini RJ, Tondo L (2008) Lithium and suicidal risk. Bipolar Disord, 10:114-115.

Beckman L, Perris C, Strandman E, Wählby L (1978) HLA antigens and affective disorders. Hum Hered, 28:96-99.

Berridge MJ (1989) Inositol trisphosphate, calcium, lithium, and cell signaling. JAMA, 262:1834-1841.

Campbell J, Crow RR, Goeken N, Pfohl B, Pauls D, Palmer D (1984) Affective disorder not linked to HLA in a large bipolar kindred. J Affect Disord, 7:45-51.

Can A, Schulze TG, Gould TD (2014) Molecular actions and clinical pharmacogenetics of lithium therapy. Pharmacol Biochem Behav, 123:3-16.

Cazzullo CL, Smeraldi E, Penati G (1974) The leucocyte antigenic system HL-A as a possible genetic marker of schizohprenia. Br J Psychiatry, 125:25-27.

Chen CH, Lee CS, Lee MTM, Ouyang WC, Chen CC, Chong MY et al. (2014) Variant GADL1 and response to lithium therapy in bipolar I disorder. N Engl J Med, 370:119-128.

Cipriani A, Pretty H, Hawton K, Geddes JR (2005) 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, 162: 1805–1819.

Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS et al. (2011) Grand challenges in global mental health. Nature, 475:27–30.

Cousin DA, Aribisala B, Ferrier IN, Blamire AM (2013) Lithium, gray matter, and magnetic resonance imaging signal. Biol Psychiatry, 73:652-657.

Curran G, Ravindran A (2014) Lithium for bipolar disorder: a review of the recent literature. Expert Rev Neurother, 14:1079-1098.

Davanzo P, Thomas MA, Yue K, Oshiro T, Belin T, Strober M et al. (2001) Decreased anterior cingulate myo-inositol/creatine spectroscopy resonance with lithium treatment in children with bipolar disorder. Neuropsychopharmacology, 24:359-369.

Debnath M, Busson M, Jamain S, Etain B, Hamdani N, Oliveira J et al. (2013) The HLA-G low expressor genotype is associated with protection against bipolar disorder. Human Immunol, 74:593-597.

Del Vecchio M, Farzati B, Maj M, Minucci P, Guida L, Kemali D (1981) Cell membrane predictors of response to lithium prophylaxis of affective disorders. Neuropsychobiology, 7:243-247.

Dubovsky SL, Franks RD (1983) Intracellular calcium ions in affective disorders: a review and an hypothesis. Biol Psychiatry, 18:781-797.

Emamghoreishi M, Schlichter L, Li PP, Parikh S, Sen J, Kamble A et al. (1997) High intracellular calcium concentrations in transformed lymphoblasts from subjects with bipolar I disorder. Am J Psychiatry, 154:976-982.

Fleck DE, Ernest N, Adler CM, Cohen K, Eliassen JC, Norris M, et al. (2017) Prediction of lithium response in first-episode mania using the LITHium Intelligent Agent (LITHIA): pilot data and proof-of-concept. Bipolar Disord, 19:259-272.

Foland LC, Altshuler LL, Sugar CA, Lee AD, Leow AD, Townsend J (2008) Increased volume of the amygdala and hippocampus in bipolar patients treated with lithium. Neuroreport, 19:221-224.

Fountoulakis KN, Vieta E, Young A, Yatham L, Grunze H, Blier P (2017) The International College of Neuropsychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), part 4: unmet needs in the treatment of bipolar disorder and recommendations for future research. Int J Neuropsychopharmacol, 20:196-205.

Frazer A, Mendels J, Brunswick D, London J, Pring M, Ramsey TA (1978) Erythrocyte concentrations of the lithium ion: clinical correlates and mechanisms of action. Am J Psychiatry, 135:1065-1069.

Friedman SD, Dager SR, Parow A, Hirashima F, Demopulos C, Stoll AL et al. (2004) Lithium and valproic acid treatment effects on brain chemistry in bipolar disorder. Biol Psychiatry, 56:340-348.

Garnham J, Munro A, Slaney C, MacDougall M, Passmore M, Duffy A et al. (2007) Prophylactic treatment response in bipolar disorder: results of a naturalistic observation study. J Affective Disord, 104:185-190.

Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM (2004) Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry, 161:217-222.

Goldin LR, Clerget-Darpoux F, Gershon ES (1982) Relationship of HLA to major affective disorder not supported. Psychiatry Res, 7: 29-45.

Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D (2003) Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA, 290:1467–1473.
Goodwin FK, Jamison KR (2007) Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression, 2nd edition. New York, Oxford University Press.
Gould TD (2006) Targeting glycogen synthase kinase-3 as an approach to develop novel mood-stabilising medications. Expert Opin Ther Targets, 10:377-392.
Green EK, Raybould R, Macgregor S, Hyde S, Young AH, O'donovan MC et al. (2006) Genetic variation of brain-derived neurotrophic factor (BDNF) in bipolar disorder. Br J Psychiatry, 188:21-25.
Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M et al. (2002) Is response to prophylactic lithium a familial trait? J Clin Psychiatry, 63:942-947.
Grof P, Müller - Oerlinghausen B (2009) A critical appraisal of lithium's efficacy and effectiveness: the last 60 years. Bipolar Disord, 11:10-19.
Gülöksüz S, Altınbaş K, Çetin EA, Kenis G, Gazioğlu SB, Deniz G et al. (2012). Evidence for an association between tumor necrosis factor-alpha levels and lithium response. J Affect Disord, 143:148-152.
Hajek T, Cullis J, Novak T, Kopecek M, Blagdon R, Propper L (2013) Brain structural signature of familial predisposition for bipolar disorder: replicable evidence for involvement of the right inferior frontal gyrus. Biol Psychiatry, 73:144-152.
Hayes JF, Miles J, Walters K (2015) A systematic review and metaanalysis of premature mortality in bipolar affective disorder. Acta Psychiatr Scand, 131:417–425.
Ikeda A, Kato T (2003) Biological predictors of lithium response in bipolar disorder. Psychiatry Clinical Neurosci, 57:243-250.
Jefferson JM, Greist JH (2000) Lithium. In Comprehensive Textbook of Psychiatry (Eds B Sadock, V Sadock):2377-2390. Baltimore, Lippincott William Wilkins.
Johnson GFS, Hunt GE, Robertson S, Doran TJ (1981) A linkage study of manic-depressive disorder with HLA antigens, blood groups, serum proteins and red cell enzymes. J Affect Disord, 3:43-58.
Kato T, Fujii K, Kamiya A, Kato N (2000) White matter hyperintensity detected by magnetic resonance imaging and lithium response in bipolar disorder: a preliminary observation. Psychiatry Clin Neurosci, 54:117-120.
Kato T, Inubushi T, Kato N (2000) Prediction of lithium response by 31P-MRS in bipolar disorder. Int J Neuropsychopharmacol, 3:83-85.
Kato T, Inubushi T, Takahashi S (1994) Relationship of lithium concentrations: in the brain measured by lithium-7: magnetic resonance spectroscopy to: treatment response in mania. J Clin Psychopharmacol, 14:330-335.
Kato T, Murashita J, Kamiya A, Shioiri T, Kato N, Inubushi T (1998) Decreased brain intracellular pH measured by 31 P-MRS in bipolar disorder: a confirmation in drug-free patients and correlation with white matter hyperintensity. Eur Arch Psychiatry Clin Neurosci, 248:301-306.
Kato T, Shioiri T, Inubushi T, Takahashi S (1993) Brain lithium concentrations measured with lithium-7 magnetic resonance spectroscopy in patients with affective disorders: relationship to erythrocyte and serum concentrations. Biol Psychiatry, 33:147-152.
Kato T, Takahashi S, Inubushi T (1992) Brain lithium concentration by 7 li-and 1 h-magnetic resonance spectroscopy in bipolar disorder. Psychiatry Res, 45:53-63.
Kessing LV, Hellmund G, Andersen PK (2011) Predictors of excellent response to lithium: results from a nationwide register-based study. Int Clin Psychopharmacol, 26:323-328.
Kessing LV, Vradi E, Andersen PK (2014) Starting lithium prophylaxis early v. late in bipolar disorder. Br J Psychiatry, 205:214-220.
Kleindienst N, Engel RR, Greil W (2005) Which clinical factors predict response to prophylactic lithium? a systematic review for bipolar disorders. Bipolar Disord, 7:404-417.
Komoroski RA, Newton JEO, Walker E, Cardwell D, Jagannathan NR, Ramaprasad et al (1990) In Vivo NMR spectroscopy of lithium-7 in humans. Magn Reson Med, 15:347-356.
Kulhara P, Basu D, Mattoo SK, Sharan P, Chopra R (1999) Lithium prophylaxis of recurrent bipolar affective disorder: long-term outcome and its psychosocial correlates. J Affect Disord, 54:87-96.
Kusumi I, Koyama T, Yamashita I (1994) Serotonin-induced platelet intracellular calcium mobilization in depressed patients. Psychopharmacology, 113:322-327.
Kusumi I, Suzuki K, Sasaki Y, Kameda K, Koyama T (2000) Treatment response in depressed patients with enhanced Ca mobilization stimulated by serotonin. Neuropsychopharmacology, 23:690-696.
Licht RW, Vestergaard P, Brodersen A (2008) Long - term outcome of patients with bipolar disorder commenced on lithium prophylaxis during hospitalization: a complete 15-year register-based follow-up. Bipolar Disord, 10:79-86.
Lopez AD, Murray CC (1998) The global burden of disease, 1990– 2020. Nat Med 4: 1241–1243.

Luca A, Calandra C, Luca M (2016) Gsk3 signalling and redox status in bipolar disorder: evidence from lithium efficacy. Oxid Med Cellular Longev, 2016:3030547.

Maj M, Arena F, Lovero N, Pirozzi R, & Kemali D (1985) Factors associated with response to lithium prophylaxis in DSM III major depression and bipolar disorder. Pharmacopsychiatry, 18:309-313.

Maj M, Vecchio M, Starace F, Pirozzi R, Kemali D (1984) Prediction of affective psychoses response to lithium prophylaxis. Acta Psychiatr Scand, 69:37-44.

Malhi GS, Outhred T (2016) Therapeutic mechanisms of lithium in bipolar disorder: recent advances and current understanding. CNS Drugs, 30:931-949.

Manchia M, Adli M, Akula N, Ardau R, Aubry JM, Backlund L et al. (2013) Assessment of response to lithium maintenance treatment in bipolar disorder: a Consortium on Lithium Genetics (ConLiGen) report. PloS One, 8:e65636.

Manji H K, Potter WZ, Lenox RH (1995) Signal transduction pathways: molecular targets for lithium's actions. Arch Gen Psychiatry, 52:531-543.

Masui T, Hashimoto R, Kusumi I, Suzuki K, Tanaka T, Nakagawa S et al. (2006). A possible association between the− 116C/G single nucleotide polymorphism of the XBP1 gene and lithium prophylaxis in bipolar disorder. Int J Neuropsychopharmacol, 9:83-88.

Masui T, Hashimoto R, Kusumi I, Suzuki K, Tanaka T, Nakagawa S et al. (2006) Lithium response and Val66Met polymorphism of the brain-derived neurotrophic factor gene in Japanese patients with bipolar disorder. Psychiatr Genet, 16:49-50.

McCarthy MJ, Leckband SG, Kelsoe JR (2010) Pharmacogenetics of lithium response in bipolar disorder. Pharmacogenomics, 11:1439-1465.

Meltzer HL (1986) Lithium mechanisms in bipolar illness and altered intracellular calcium functions. Biol Psychiatry, 21:492-510.

Mendels J, Frazer A (1973) Intracellular lithium concentration and clinical response: towards a membrane theory of depression. J Psychiatr Res, 10:9-18.

Mendlewicz J (1979) Prediction of treatment outcome: family and twin studies in lithium prophylaxis and the question of lithium red blood cell/plasma ratios. Lithium. Controversies and Unresolved Issues. Excerpta Medica: Amsterdam.

Mendlewicz J, Verbanck P, Linkowski P, Wilmotte J (1978) Lithium accumulation in erythrocytes of manic-depressive patients: an in vivo twin study. Br J Psychiatry, 133:436-444.

Michelon L, Meira-Lima I, Cordeiro Q, Miguita K, Breen G, Collier D et al. (2006) Association study of the INPP1, 5HTT, BDNF, AP-2β and GSK-3β GENE variants and restrospectively scored response to lithium prophylaxis in bipolar disorder. Neurosci Lett, 403:288-293.

Moore CM, Breeze JL, Gruber SA, Babb SM, deB Frederick B, Villafuerte RA et al. (2000) Choline, myo - inositol and mood in bipolar disorder: a proton magnetic resonance spectroscopic imaging study of the anterior cingulate cortex. Bipolar Disord, 2:207-216.

Moore GJ, Bebchuk JM, Wilds IB, Chen G, Menji HK (2000) Lithium-induced increase in human brain grey matter. Lancet, 356:1241-1242.

Murashita J, Kato T, Shioiri T, Inubushi T, Kato N (2000) Altered brain energy metabolism in lithium-resistant bipolar disorder detected by photic stimulated 31 P-MR spectroscopy. Psychol Med, 30:107-115.

Müller-Oerlinghausen B, Müser-Causemann B, Volk J (1992) Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. J Affect Disord, 25:261-269.

National Institute for Health and Care Excellence (NICE) (2014) Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care. London, NICE.

Nemanov L, Ebstein RP, Belmaker RH, Osher Y, Agam G (1999) Effect of bipolar disorder on lymphocyte inositol monophosphatase mRNA levels. Int J Neuropsychopharmacol, 2:25-29.

Noworolski SM, Nelson SJ, Henry RG, Day MR, Wald LL, Star - Lack J et al. (1999) High spatial resolution 1H - MRSI and segmented MRI of cortical gray matter and subcortical white matter in three regions of the human brain. Magn Reson Med, 41:21-29.

Perlis RH, Smoller JW, Ferreira MA, McQuillin A, Bass N, Lawrence J et al. (2009) A genomewide association study of response to lithium for prevention of recurrence in bipolar disorder. Am J Psychiatry, 166:718-725.

Perris C, Strandman E, Wählby L (1979) HL-A antigens and the response to prophylactic lithium. Neuropsychobiology, 5: 114-118.

Pfennig A, Alda M, Young T, MacQueen G, Rybakowski J, Suwalska A et al. (2014) Prophylactic lithium treatment and cognitive performance in patients with a long history of bipolar illness: no simple answers in complex disease-treatment interplay. Int J Bipolar Disord, 2:16.

Pfennig A, Schlattmann P, Alda M, Grof P, Glenn T, Müller - Oerlinghausen B et al. (2010) Influence of atypical features on the quality of prophylactic effectiveness of long-term lithium treatment in bipolar disorders. Bipolar Disord, 12:390-396.

Renshaw PF, Wicklund S (1988) In vivo measurement of lithium in humans by nuclear magnetic resonance spectroscopy. Biol Psychiatry, 23:465-475.

Rohayema J, Bayléb JF, Richaa S (2008) Prédicteurs de réponse prophylactique au lithium Predictors of prophylactic response to lithium. L'Encéphale, 34, 394-399.

Rybakowski JK, Suwalska A, Skibinska M, Szczepankiewicz A, Leszczynska-Rodziewicz A, Permoda A et al. (2005) Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. Pharmacopsychiatry, 38:166-170.

Rybakowski JK, Chlopocka - Wozniak M, Suwalska A (2001) The prophylactic effect of long - term lithium administration in bipolar patients entering treatment in the 1970s and 1980s. Bipolar Disord, 3:63-67.

Rybakowski JK, Dmitrzak-Weglarz M, Dembinska-Krajewska D, Hauser J, Akiskal KK, Akiskal HH (2014) Polymorphism of circadian clock genes and temperamental dimensions of the TEMPS-A in bipolar disorder. J Affect Disord, 159:80-84.

Rybakowski JK, Dmitrzak-Weglarz M, Suwalska A, Leszczynska-Rodziewicz A, Hauser J (2009) Dopamine D1 receptor gene polymorphism is associated with prophylactic lithium response in bipolar disorder. Pharmacopsychiatry, 42:20-22.

Rybakowski JK, Skibinska M, Suwalska A, Leszczynska - Rodziewicz A, Kaczmarek L, Hauser J (2011) Functional polymorphism of matrix metalloproteinase - 9 (MMP - 9) gene and response to lithium prophylaxis in bipolar patients. Hum Psychopharmacol, 26:168-171.

Rybakowski JK, Suwalska A, Czerski PM, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Hauser J (2005) Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. Pharmacol Rep, 57:124-127.

Rybakowski JK, Suwalska A, Skibinska M, Dmitrzak - Weglarz M, Leszczynska - Rodziewicz A, Hauser J (2007) Response to lithium prophylaxis: interaction between serotonin transporter and BDNF genes. Am J Med Genet B Neuropsychiatr Genet, 144:820-823.

Ryder LP, Nielsen LS, Svejgaard A (1974) Associations between HL-A histocompatibility antigens and non-malignant diseases. Humangenetik, 25:251-264.

Sachs GS, Renshaw PF, Lafer B, Stoll AL, Guimarães AR, Rosenbaum JF et al. (1995) Variability of brain lithium levels during maintenance treatment: a magnetic resonance spectroscopy study. Biol Psychiatry, 38:422-428.

Schou M (2001) Lithium treatment at 52. J Affect Disord, 67:21-32.

Schulze T (2012) The consortium on lithium genetics (ConLiGen) genome-wide association studies of lithium response phenotypes in bipolar disorder. CINP congress, 3-7 June 2012 Stockholm, p: 36.

Schulze TG, Alda M, Adli M, Akula N, Ardau R, Bui ET et al. (2010) 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, 62:72-78.

Serretti A, Lilli R, Lorenzi C, Franchini L, Di Bella D, Catalano M et al. (1999a) Dopamine receptor D2 and D4 genes, GABA A alpha-1 subunit gene and response to lithium prophylaxis in mood disorders. Psychiatry Res, 87:7-19.

Serretti A, Lilli R, Lorenzi C, Franchini L, Smeraldi E (1998) Dopamine receptor D3 gene and response to lithium prophylaxis in mood disorders. Int J Neuropsychopharmacol, 1:125-129.

Serretti A, Lilli R, Lorenzi C, Gasperini M, Smeraldi E (1999) Tryptophan hydroxylase gene and response to lithium prophylaxis in mood disorders. J Psychiatr Res, 33:371-377.

Serretti A, Lilli R, Mandelli L, Lorenzi C, Smeraldi E (2001) Serotonin transporter gene associated with lithium prophylaxis in mood disorders. Pharmacogenomics J, 1:71-77.

Serretti A, Lorenzi C, Lilli R, Mandelli L, Pirovano A, Smeraldi E (2002) Pharmacogenetics of lithium prophylaxis in mood disorders: Analysis of COMT, MAO - A, and G β 3 variants. Am J Med Genet, 114:370-379.

Serretti A, Lorenzi C, Lilli R, Smeraldi E (2000) Serotonin receptor 2A, 2C, 1A genes and response to lithium prophylaxis in mood disorders. Journal of psychiatric research, 34:89-98.

Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M et al. (2014) Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. Int J Bipolar Disord, 2:15.

Shaldubina A, Agam G, Belmaker RH (2001) The mechanism of lithium action: state of the art, ten years later. Prog Neuro-Psychopharmacol Biol Psychiatry, 25:855-866.

Shapiro RW, Bock E, Rafaelsen O J, Ryder LP, Svejgaard A (1976) Histocompatibility antigens and manic-depressive disorders. Arch Gen Psychiatry, 33:823-825.

Shapiro RW, Ryder LP, Svejgaard A, Rafaelsen OJ (1977) HLA antigens and manic-depressive disorders: further evidence of an association. Psychol Med, 7:387-396.

Silberberg G, Levit A, Collier D, Clair DS, Munro J, Kerwin RW et al. (2008) Stargazin involvement with bipolar disorder and response to lithium treatment. Pharmacogenet Genomics, 18:403-412.

Silverstone PH, McGrath BM (2009) Lithium and valproate and their possible effects on the myo-inositol second messenger system in healthy volunteers and bipolar patients. Int Rev Psychiatry, 21:414-423.

Silverstone PH, Wu RH, O'donnell T, Ulrich M, Asghar SJ, Hanstock CC (2003) Chronic treatment with lithium, but not sodium valproate, increases cortical N-acetyl-aspartate concentrations in euthymic bipolar patients. Int Clin Psychopharmacol, 18:73-79.

Sklar P, Gabriel SB, McInnis MG, Bennet P, Lim YM, Tsan G et al. (2002) Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Mol Psychiatry, 7:579-593.

Soares JC, Krishnan KRR, Keshavan MS (1996) Nuclear magnetic resonance spectroscopy: new insights into the pathophysiology of mood disorders. Depression, 4: 14-30.

Sportiche S, Geoffroy PA, Brichant-Petitjean C, Gard S, Khan JP, Azorin M (2017) Clinical factors associated with lithium response in bipolar disorders. Aust N Z J Psychiatry, 51:524-530.

Squassina A, Congiu D, Manconi F, Manchia M, Chillotti C, Lampus S et al. (2008) The PDLIM5 gene and lithium prophylaxis: an association and gene expression analysis in Sardinian patients with bipolar disorder. Pharmacol Res, 57:369-373.

Squassina A, Manchia M, Borg J, Congiu D, Costa M, Georgitsi M et al. (2011) Evidence for association of an ACCN1 gene variant with response to lithium treatment in Sardinian patients with bipolar disorder. Pharmacogenomics, 12:1559-1569.

Steeir VM, Lovlie R, Osher Y, Belmaker RH, Berle JO, Gulbrandsen AK (1998) The polymorphic inositol polyphosphate 1-phosphatase gene as a candidate for pharmacogenetic prediction of lithium-responsive manic-depressive illness. Pharmacogenetics, 8:259-268.

Suzuki K, Kusumi I, Sasaki Y, Koyama T (2001) Serotonin-induced platelet intracellular calcium mobilization in various psychiatric disorders: is it specific to bipolar disorder? J Affect Disord, 64:291-296.

Swayze VW, Andreasen NC, Alliger RJ, Ehrhardt JC, Yuh WT (1990) Structural brain abnormalities in bipolar affective disorder: ventricular enlargement and focal signal hyperintensities. Arch Gen Psychiatry, 47:1054-1059.

Szczepankiewicz A, Skibinska M, Suwalska A, Hauser J, Rybakowski JK (2009) The association study of three FYN polymorphisms with prophylactic lithium response in bipolar patients. Hum Psychopharmacol, 24:287-291.

Tan D, Özerdem A, Güntekin B, Atagün MI, Tülay E, Karadağ F et al. (2016) Increased beta frequency (15-30 hz) oscillatory responses in euthymic bipolar patients under lithium monotherapy. Clin EEG Neuroscience, 47:87-95.

Targum SD, Gershon ES, Van Eerdewegh M, Rogentine N (1979) Human leukocyte antigen system not closely linked to or associated with bipolar manic-depressive illness. Biol Psychiatry, 14:615-636.

Tighe SK, Mahon PB, Potash JB (2011) Predictors of lithium response in bipolar disorder. Ther Adv Chronic Dis, 2:209-226.

Tobe BT, Crain AM, Winquist AM, Calabrese B, Makihara H, Zhao WN et al. (2017) Probing the lithium-response pathway in hiPSCs implicates the phosphoregulatory set-point for a cytoskeletal modulator in bipolar pathogenesis. Proc Natl Acad Sci U S A, 114: E4462-E4471.

Tondo L, Baldessarini RJ, Floris G (2001) Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. Br J Psychiatry, 178:s184-s190.

Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Ahrens B et al. (1998) Evidence for a role of phospholipase C-γ1 in the pathogenesis of bipolar disorder. Mol Psychiatry, 3:534-538.

Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Ahrens B et al. (1999) MAOA: association and linkage studies with lithium responsive bipolar disorder. Psychiatr Genet, 9:13-16.

Turecki G, Grof P, Grof E, D'souza V, Lebuis L, Marineau C et al. (2001) Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry, 6:570-578.

Usher J, Menzel P, Schneider-Axmann T, Kemmer C, Reith W, Falkai P et al. (2010) Increased right amygdala volume in lithium - treated patients with bipolar I disorder. Acta Psychiatr Scand, 121:119-124.

Ünal A, Çöpoğlu ÜS, Bülbül F, Vırıt O, Savaş HA (2013) Lityumun kırk yıldır sorunsuz kullanımı: olgu sunumu. Journal of Mood Disorders, 3:70-73.

Ventura T, Lobo A, Marco JC (1990) HLA antigens in bipolar affective patients. Actas Luso Esp Neurol Psiquiatr Cienc Afines, 18:339-343.

Vernon AC, Hajek T (2013) Effects of lithium on magnetic resonance imaging signal might not preclude increases in brain volume after chronic lithium treatment. Biol Psychiatry, 74:e39-e40.

Washizuka S, Ikeda A, Kato N, Kato T (2003) Possible relationship between mitochondrial DNA polymorphisms and lithium response in bipolar disorder. Int J Neuropsychopharmacol, 6:421-424.

Williams RSB, Eames M, Ryves WJ, Viggars J, Harwood AJ (1999) Loss of a prolyl oligopeptidase confers resistance to lithium by elevation of inositol (1, 4, 5) trisphosphate. EMBO J, 18:2734-2745.

Yamawaki S, Kagaya A, Tawara Y, Inagaki M (1998) Intracellular calcium signaling systems in the pathophysiology of affective disorders. Life Sci, 62:1665-1670.

Yatham LN, Fountoulakis KN, Rahman Z, Ammerman D, Fyans P, Marler SV et al. (2013a) Efficacy of aripiprazole versus placebo as adjuncts to lithium or valproate in relapse prevention of manic or mixed episodes in bipolar I patients stratified by index manic or mixed episode. J Affect Disord, 147:365–372.

Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M et al. (2013b) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord, 15:1-44.

Yoon IS, Li PP, Siu KP, Kennedy JL, Cooke RG, Parikh SV et al. (2001) Altered IMPA2 gene expression and calcium homeostasis in bipolar disorder. Mol Psychiatry, 6:678-683.

Young AH, Hammond JM (2007) Lithium in mood disorders: increasing evidence base, declining use? Br J Psychiatry, 191:474-476.

Yucel K, McKinnon MC, Taylor VH, Macdonald K, Alda M, Young LT et al. (2007) Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. Psychopharmacology, 195:357-367.

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