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Response to Lithium in Bipolar Disorder: Clinical and Genetic Findings

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ABSTRACT: The use of lithium is a cornerstone for preventing recurrences in bipolar disorder (BD). The response of patients with bipolar disorder to lithium has different levels of magnitude. About one-third of lithium-treated patients are excellent lithium responders (ELR), showing total prevention of the episodes. A number of clinical characteristics were delineated in patients with favorable response to lithium as regards to clinical course, family history of mood disorders, and psychiatric comorbidity. We have also demonstrated that temperamental features of hypomania (a hyperthymic temperament) and a lack of cognitive disorganization predict the best results of lithium prophylaxis. A degree of prevention against manic and depressive episodes has been regarded as an endophenotype for pharmacogenetic studies. The majority of data have been gathered from so-called "candidate" gene studies. The candidates were selected on the basis of neurobiology of bipolar disorder and mechanisms of lithium action including, among others, neurotransmission, intracellular signaling, neuroprotection or circadian rhythms. We demonstrated that response to lithium has been connected with the genotype of *BDNF* gene and serum BDNF levels and have shown that ELR have normal cognitive functions and serum BDNF levels, even after long-term duration of the illness. A number of genome-wide association studies (GWAS) of BD have been also performed in recent years, some of which also focused on lithium response. The Consortium on Lithium Genetics (ConLiGen) has established the large sample for performing the genome-wide association study (GWAS) of lithium response in BD, and the first results have already been published.

KEYWORDS: *Lithium, bipolar disorder, efficacy, clinical factors, genetic factors*

LITHIUM AS A MOOD-STABILIZING DRUG

Bipolar disorder (BD), for which principal symptoms constitute recurrent manic and depressive episodes, is a serious mental illness, with a worldwide prevalence of 2−5% of the population.[1] BD imposes a great burden on both patients and their families, and approximately 10−20% of patients commit suicide over the course of their illness.[2] In a recent fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, bipolar disorder makes a separate category, with main clinical differentiation based on the severity of manic episodes into bipolar I, with full-blown manic episodes, and bipolar II, with hypomanic ones.[3]

In the treatment of bipolar disorder, mood stabilizing drugs play the most important role. A mood stabilizer can be defined as a drug that, if used as monotherapy, (1) acts therapeutically in mania or/and in depression; (2) acts prophylactically against manic or/and depressive episodes, as demonstrated in a trial of at least one year's duration, and (3) does not worsen any therapeutic or prophylactic aspect of the illness outlined above. The antimanic effect of lithium was first observed by the Australian psychiatrist, John Cade, 65 years ago,[4] and its mood-stabilizing efficacy (preventing manic and depressive recurrences in mood disorders) was described in the early 1960s by the British psychiatrist, Geoffrey Hartigan.[5] In 1970−1973, the results were published of eight controlled studies researching the prophylactic effectiveness of lithium and including the use of placebo carried out in Europe (in Denmark and the U.K.) and in the United States. Analysis showed that the percentage of patients in whom recurrences of depression or mania occurred was significantly lower while receiving lithium (on average 30%) than while receiving placebo (on average 70%).[6]

The prophylactic effectiveness of lithium has been confirmed in two meta-analyses performed in the first decade of the 21th century. Geddes et al.,[7] covering 5 randomized controlled trials involving 770 patients, showed that lithium was more effective than a placebo in preventing all relapses, with a relative risk (RR) of 0.65, being slightly better against manic recurrences (RR = 0.62) than against depressive recurrences (RR = 0.72). Nivoli et al.[8] performed a systematic research of long-term treatment randomized controlled trials enrolling 1561 bipolar patients with at least 6 months of follow-up, of whom 534 were randomized to lithium. They concluded that, while earlier studies suggested a high effectiveness of lithium against both mania and depression, more recent ones show greater evidence of the effectiveness of lithium prophylaxis against manic relapses. Nowadays, lithium is still regarded as the cornerstone of the long-term therapy of bipolar disorder.[9]

Fifty years after John Cade's paper,[4] the Canadian psychiatrist, Paul Grof,[10] introduced the term "excellent lithium responders" for patients responding to lithium monotherapy by

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not having further recurrences of the illness and thus able to live a totally normal life. In our study on bipolar patients entering lithium prophylaxis in the 1970s (60 patients) and in the 1980s (49 patients), the percentage of patients not experiencing affecting episodes on lithium monotherapy for over a 10 year period was 35% and 27%, respectively, roughly one-third of lithium-treated subjects.[11]

A degree of prevention against recurrences of manic and depressive episodes during long-term lithium treatment can be assessed either retrospectively or prospectively, and the response can be expressed in either categorical or dimensional terms. The most frequent categorical assessment consists of three categories: (1) excellent lithium responders (ER), no affective episodes on lithium; (2) partial lithium responders (PR,: 50% reduction in the episode index, defined as number of episodes per year compared to prelithium period; (3) lithium nonresponders (NR), <50% reduction, no change or worsening in the episode index, defined as number of episodes per year compared to prelithium period.

In 2002, the Canadian researchers (Alda et al.) introduced a scale allowing quantitative retrospective assessment of the quality of prophylactic lithium response.[12] This scale is referred to as "the Alda scale". 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 off the treatment; B2, frequency of episode off 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. The total score is obtained by subtracting B from A and is in the range 0−10. Therefore, this scale allows for either a categorical assessment (i.e., below or above some cutoff point) or a dimensional assessment of lithium response.

The stability of lithium response over time has been a subject of considerations. In his recent review, Post[13] presents two different forms of acquired treatment resistance to lithium. The first is a refractoriness due to discontinuation of lithium after a good long-term response. In such cases, the next recurrence does not favorably respond to lithium used in previously effective doses. The second is a refractoriness due to a possible tolerance to lithium. In such cases, after a good long-term response, the affective episodes appear, sometimes of increased severity, frequency, and duration. However, in a recent multicenter study including 346 lithium-treated patients, it was found that the mean morbidity index in this group remained stable over a period of 20 years.[14]

A great deal of research has been performed trying to elucidate clinical and genetic factors connected with lithium efficacy, with the assessment of such efficacy by the three categories or/and the Alda scales. A degree of prevention against recurrences of manic and depressive episodes during long-term lithium treatment (e.g., excellent lithium responders) was regarded as an endophenotype for pharmacogenetic studies.

CLINICAL FACTORS ASSOCIATED WITH LITHIUM EFFICACY

In 2010, Grof,[15] summarizing the issue of excellent lithium responders pointed to such clinical features of this group as the illness course with distinct affective episodes and periods of complete remission. He also noticed that these patients have low psychiatric comorbidity and frequent bipolar family history. Their clinical picture would thus reflect a "classic" form of the bipolar disorders, whose features are similar to those described by Kraepelin[16] as *manisch-depressives Irresein*.

Five years earlier, a meta-analysis of clinical factors associated with lithium efficacy was performed by Kleindienst et al.[17] The authors investigated 42 potential clinical predictors of lithium prophylactic efficacy based on the results of 43 studies. Two factors connected with better effect of lithium were identified, namely, an episodic pattern of mania-depression sequences and later age of illness onset. On the other hand, three factors were found which may weaken the prophylactic effect of lithium, such as an episodic pattern of depression-mania sequence, a high number of previous hospitalizations, and continuous cycling. This may indicate that lithium efficacy is related to a predominant manic pole as well as to lower severity of the disorder.

There are also studies comparing lithium responders with those responding favorably to other mood-stabilizing drugs. In the German Multicenter Study of Long-Term Treatment of Affective and Schizoaffective Psychoses (the MAP study) comparing the differential efficacy of lithium versus carbamazepine in a randomized clinical trial with an observation period of 2.5 years, patients with the classical form of the illness (bipolar I without mood-incongruent delusions and without comorbidity) had the prophylactic efficacy of lithium superior to that of carbamazepine, while the opposite was true for patients with the nonclassical form of the illness.[18] Therefore, it may be suggested that carbamazepine responders may have an atypical bipolar disorder, characterized by mood-incongruent delusions and comorbidity. It is likely that the clinical features of responders to carbamazepine are similar to those of another mood-stabilizing anticonvulsant drug, valproate.

In a study attempting to delineate clinical and family history features of responders to lamotrigine, in contrast to responders to lithium, it was found that the course of illness in lamotrigine responders was rapid cycling or chronic, while episodic in responders to lithium, and lamotrigine-responders had higher comorbidity of panic disorder and substance abuse compared to lithium responders. The relatives of lithium responders had a significantly higher risk of bipolar disorder, while relatives of lamotrigine responders had a higher prevalence of schizoaffective disorder, major disorder, and panic attacks.[19]

In our recent study,[20] we included 111 patients (76 women, 35 men) with bipolar disorder, aged 34−85 years (mean 61 years), receiving lithium for 5−39 years (mean 18 years). Bipolar I was diagnosed in 79 patients, and diagnosis of bipolar II was made in 32 patients. Lithium efficacy was assessed by the three-category scale, identifying excellent responders (ER), partial responders (PR), and nonresponders (NR), as well as with the Alda Scale, estimating efficacy within the range 0−10. Among patients studied, 27% met criteria for ER, 63% for PR, and 10% for NR and the mean score in Alda scale was 6.6 ± 2.5.

The results of our study confirmed some factors, previously suggested as connected with lithium response, and contradicted the others. We confirmed better effect of lithium prophylaxis in patients with later onset of illness, shown in previous studies, covering a total of 1138 patients.[17] However, we did not find a relationship between lithium efficacy and duration of illness before lithium. This contradicts the suggestions of Franchini et al.[21] and Ketter et al.[22] about a better prophylactic effect of lithium in patients in which lithium treatment had been

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instituted within a short duration of the illness. We also found a better effect of lithium in bipolar II versus bipolar I patients, while such a difference was not found in the analysis of Kleindienst et al.[17]

The early studies of Maj et al.[23] as well as Mendlewicz et al.[24] suggested that better effect of lithium may be connected with more frequent family history of mood disorder. However, in a subsequent paper of Coryell et al.,[25] familial loading with bipolar disorder was not associated with better outcome with lithium. Our results seem to show the opposite, as patients without family history of mood disorder had significantly higher score on the Alda scale compared with those with such a history (7.0 ± 2.2 vs 5.8 ± 2.7, respectively). In this context, a paper of Misra and Burns[26] can be mentioned, where in a group of severe lithium nonresponders 3/4 of them had family history of mood disorder. On the other hand, we observed that having family members receiving lithium was connected with better prophylactic effect of lithium. Probably, a decision to start treatment with lithium in a family member was based on good efficacy of this drug in the patient. This may also confirm the opinion of Grof[15] that a favorable effect of lithium is heritable.

Young et al.[27] showed a trend toward lithium nonresponsiveness in bipolar patients with comorbid anxiety disorders. The results of our study indicate that the impact of comorbid anxiety disorders on the degree of prophylactic lithium effect may be sex-specific. We have found that men with comorbid anxiety disorders had significantly poorer response to lithium as measured with the Alda scale compared to those without (5.5 ± 2.1 vs 7.0 ± 2.2) while the opposite was true in women (7.3 ± 2.0 vs 6.3 ± 2.9, respectively).

In a study of O'Connell et al.,[28] including 248 lithium-treated bipolar patients, current alcohol and drug abuse was associated with poor outcome. In our sample, 34% of men showed different degrees of alcohol abuse/dependence, and the efficacy of lithium in this group was poorer compared with the remaining group (5.4 ± 2.2 vs 6.8 ± 2.2 respectively).

We have also performed research to delineate a specific personality profile for the best lithium response. In 71 patients treated with lithium carbonate for 5−37 years (mean 18 years), an assessment was made of their temperamental affective profiles using the Temperament Scale of the Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A),[29] and their schizotypic traits by means of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE).[30] The scores obtained on these scales were correlated with the assessment of prophylactic lithium efficacy by means of the Alda scale.

TEMPS-A measures five temperaments: depressive, cyclothymic, hyperthymic, irritable, and anxious. In our study, the response to lithium correlated significantly positively with the hyperthymic temperament score, and negatively with the anxiety, cyclothymic, and depressive temperament scores.[31] These results may confirm the studies dating back to Cade's[4] original report, which indicated a primacy of the antimanic action of lithium, and of analyses, showing a better effect of lithium in episodic patterns of mania−depression sequence.[17] Therapeutic effect of lithium is more significant in acute euphoric mania, related to hyperthymic temperament.[32] The negative correlation with a cyclothymic temperament may correspond to the worse effect of lithium in patients with continuous cycling.[17]

The subscales of the O-LIFE include unusual experiences, cognitive disorganization, introversion/anhedonia and impulsive nonconformity. A significant negative correlation of lithium efficacy with cognitive disorganization, and an insignificantly negative correlation with the remaining three subscales was demonstrated.[33] A dimension of cognitive disorganization is highly associated with "psychoticism" and increases the risk for schizophrenia and bipolar disorder with psychotic symptoms.[34] A negative correlation between a tendency to psychotic symptoms and lithium efficacy is consistent with clinical experiences which shows that lithium is devoid of antipsychotic effects.

Clinical factors connected with lithium prophylactic efficacy in BD are summarized in Table 1.

Table 1. Clinical Factors Associated with the Prophylactic Efficacy of Lithium (with appropriate references)

type of factor	positive (+) or negative (−) association with lithium response
clinical	distinct mood episodes (+)[15]
	periods of complete remission (+)[15]
	pattern of mania−depression sequence (+)[17]
	pattern of depression−mania sequence (−)[17]
	later age of illness (+)[17,20]
	high number of previous hospitalizations (−)[17]
	continuous cycling (−)[17]
	bipolar ii (+)[17]
familial	family history of mood disorder (−)[20]
	family members receiving lithium (+)[20]
comorbidity	comorbid anxiety in men (−)[20]
	comorbid anxiety in women (+)[20]
	alcohol abuse/dependence in men (−)[20]
personality	hyperthymic personality (+)[31]
	cyclothymic personality (−)[31]
	depressive personality (−)[31]
	anxious personality (−)[31]
	cognitive disorganization (schizotypy dimension) (−)[33]

GENETIC FACTORS ASSOCIATED WITH LITHIUM EFFICACY

Candidate Genes. Pharmacogenetics of response to lithium was the topic of several reviews, published in the past 5 years,[35−38] including that written by the author of this paper,[39] on which this section will be mostly based, with some additions of recent findings. The majority of data have been gathered from so-called "candidate" gene studies, the candidates being selected on the basis of neurobiology of bipolar disorder and mechanisms of lithium action. Within candidate genes, those connected with neurotransmission, intracellular signaling, neuroprotection, or circadian rhythm have been studied. In this Review, a separate subchapter will be dedicated to the brain-derived neurotrophic factor (BDNF) and its connection with lithium effects on cognition, reflecting studies performed by the author's group.

Among neurotransmitters, the serotonergic system has long been implicated in the neurobiology of bipolar disorder and the mechanism of lithium action.[40] In genetic research, a functional promoter polymorphism of the serotonin transporter gene (5-HTTLPR) located on chromosome 17q12, where a short (s) allele is connected with lower activity of the gene, has been most frequently studied. A short allele of 5-HTTLPR has been associated with a predisposition to affective disorder, both

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bipolar and unipolar[41] and with a poor response to antidepressants in a Caucasian population.[42] In several studies, including ours,[43−45] an association between the s allele and prophylactic lithium nonresponse was demonstrated. However, it was not confirmed in two subsequent papers.[46,47] Another study,[48] on a polymorphism of the gene for tryptophan hydroxylase, the enzyme of serotonin synthesis, found a marginal association with lithium response. As to dopaminergic system, Severino et al.[49] showed an association between bipolar illness and A48G polymorphism of the dopaminergic receptor D1 (DRD1) gene, located on chromosome 5q35, and we have demonstrated an association of this polymorphism with lithium response.[50] A role of the glutamatergic system in the pathogenesis of bipolar illness and the mechanisms of lithium action has also been postulated, with special emphasis on glutamate receptor NMDA (*N*-methyl-D-aspartate). However, in our study,[51] any association between three polymorphisms in the NMDA receptor 2B subunit (*GRIN2B*) gene and lithium response was not shown. The Src family, tyrosine kinase FYN, plays a key role in the interaction between brain-derived neurotrophic factor (BDNF) and the glutamatergic receptor NMDA and the *FYN* gene is located on chromosome 6q21. We showed an association between two polymorphisms of the *FYN* gene and bipolar disorder[52] and a marginal association between T/C polymorphism of this gene and lithium response.[53]

The effect of lithium on the phosphatidyl inositol (PI) intracellular signaling, has long been considered the most important mechanism of therapeutic action of this ion in bipolar disorder.[54] However, this was not markedly reflected in molecular-genetic studies of lithium response. An association with such a response was obtained with polymorphism of the inositol polyphosphate 1-phosphatase (*INPP1*) gene located on chromosome 2q32,[55] also in patients with comorbid post-traumatic stress disorder.[56] However, this was not replicated in a study by Brazilian investigators.[46] Studies on the polymorphisms of other genes connected with the PI system, such as inositol monophosphatase2 (*IMPA2*) and diacylglycerol kinase eta (*DGKH*) genes, did not find any associations with lithium response.[57,58] Another intracellular signaling system influenced by lithium is the cyclic adenosine monophosphate (cAMP) pathway. Mamdani et al.[59] performed an association study with genes for cAMP-response binding protein (CREB) and found an association between bipolar disorder and lithium response and two polymorphisms of *CREB1* gene located at chromosome 2q32−34. In connection with this, Canadian investigators recently showed that alterations in phosphorylated CREB (pCREB) signaling may constitute AN endophenotype of lithium-responsive bipolar disorder.[60]

Compelling evidence suggests that, in the mechanisms of lithium action in bipolar disorder, the inhibition of glycogen synthase kinase 3beta (GSK3β), the enzyme involved in neuroprotection (synaptic plasticity, apoptosis) as well as in the circadian cycle, may play an important role.[61] Italian investigators demonstrated an association between functional -50 T/C polymorphism of the *GSK3β* gene located on chromosome 3q13, and lithium response[62] but this was not confirmed in two other studies, including ours.[46,63] In a network coordinating circadian rhythms, GSK3β interacts with a number of proteins, including Rev-Erb-α, and a variant of the *Rev-Erb-α* gene, located on chromosome 17q11, has been shown, in two recent studies, to be associated with prophylactic lithium response.[64,65]

In the Poznan center, a molecular-genetic study of multiple polymorphisms of circadian rhythm genes such as *CLOCK* (circadian locomotor output cycle kaput), *ARNTL* (aryl hydrocarbon receptor nuclear translocator-like, *TIM* (timeless circadian clock), and *PER3* (period circadian clock 3) was carried out in relation to the efficacy of lithium prophylaxis. An association was found between both polymorphisms and haplotypes of the *ARNTL* and *TIM* genes (chromosome locations 11p15 and 12q13, respectively), and lithium response.[66]

Also in our Department, we carried out genetic studies on matrix metalloproteinase-9 (MMP-9), extracellularly acting endopeptidase, implicated in a number of pathological conditions including cancer, cardiovascular and neuropsychiatric diseases. We demonstrated an association between functional polymorphism of the *MMP-9* gene, located on chromosome 20q11−13, and bipolar disorder.[67] However, we were unable to find such an association with lithium response.[68] On the other hand, we did find an association with polymorphism of the glucocorticoid receptor (*NR3C1*) gene located on chromosome 5q31−32,[69] implicated in the pathogenesis of bipolar disorder.[70]

Positive results have been obtained concerning associations of three genes located on chromosome 22q11−13 with lithium response. A significant association between lithium response and genetic variations in the breakpoint cluster region (*BCR*) gene located on chromosome 22q11[71] and with the X-box binding protein 1 (*XBP1*) gene located on chromosome 22q12[72] was found. A predisposition to bipolar disorder connected with both these genes had been previously reported.[73,74] Silberberg et al[75] described an association with lithium response and the calcium channel gamma-2 subunit (*CACNG2*) gene, also known as stargazin, located on chromosome 22q13.

In conclusion, candidate gene studies mentioned above have shown a number of associations between the polymorphism of a given gene and a prophylactic response to lithium. The apparent limitation is that, only a minority of them has been consistently replicated. Furthermore, each of the single nucleotide polymorphisms of a given gene accounts for a small portion of the total variance in lithium response (1−2% at best). Therefore, lithium response is apparently polygenic, and only by simultaneously examining multiple genes and multiple variants within these genes would it be possible to provide some guidelines for predicting the response.

Brain-Derived Neurotrophic Factor (BDNF) System and Lithium Response. Brain-derived neurotrophic factor (BDNF) is the most important neurotrophic factor studied in psychiatry. It is involved in a number of brain processes including neuronal proliferation, synaptic plasticity, memory, and learning. The functional polymorphism of the *BDNF* gene, located on chromosome 11p13, shows an association with a predisposition to bipolar disorder.[76] Studies performed by our research group have shown that the response to lithium may be connected both with Val66Met polymorphism of the *BDNF* gene as well as with serum BDNF levels. Our group was the first to demonstrate an association of this polymorphism with lithium response: a better effect of lithium prophylaxis was connected with the presence of the Met allele of Val66Met BDNF polymorphism.[77,78] Interestingly, an association with the Met allele of this polymorphism was also found for hyperthymic temperament,[79] which may further confirm the results of correlation between lithium response and TEMPS-A

Table 2. Genetic Factors Associated with the Prophylactic Efficacy of Lithium (with appropriate references)

type of research	gene	chromosome location
candidate gene studies	serotonin transporter gene[43−45]	17q12
	dopaminergic receptor D1 (*DRD1*) gene[50]	5q35
	tyrosine kinase *FYN* gene[53]	6q21
	inositol polyphosphate 1-phosphatase (*INPP1*) gene[55,56]	2q32
	cAMP response binding protein (*CREB*) gene[59]	2q32−34
	glycogen synthase kinase 3 beta (*GSK3β*) gene[62]	3q13
	Rev-Erb-α gene[64,65]	17q11
	aryl hydrocarbon receptor nuclear translocator like (*ARNTL*) gene[66]	11p15
	timeless circadian clock (*TIM*) gene[66]	12q13
	glucocorticoid receptor (*NR3C1*) gene[69]	5q31−32
	breakpoint cluster region (*BCR*) gene[71]	22q11
	X-box binding protein 1 (*XBP1*) gene[72]	22q12
	calcium channel-gamma-2 subunit (*CACNGG2*) gene[75]	22q13
	brain-derived neurotrophic factor (*BDNF*) gene[77,78]	11p13
genome-wide association studies	glutamate AMPA receptor (*GRIA2*) gene[94]	4q32
	amiloride-sensitive cation channel 1 neuronal (*ACCN1*) gene[95]	17q12
	glutamate decarboxylase-like protein 1 (*GADL1*) gene[96]	3p24
	sodium bicarbonate transporter (*SLC4A10*) gene[99]	2q24

temperaments mentioned earlier.[31] We also observed an interaction between *BDNF* gene and serotonin transporter (*5-HTTLPR*) polymorphism, where the concomitant presence of Val homozygosity of *BDNF* and the s allele of *5-HTTLPR* could predict lithium nonresponse with a 70% probability.[80] On the other hand, an association of lithium response with Val66Met polymorphism of the *BDNF* gene was not confirmed in populations other than Caucasian.[46,81]

We have also studied the BDNF system in relation to cognitive functions in lithium-treated patients. It was shown in experimental studies that lithium produces an enhancement of learning and memory.[82,83] On the other hand, some degree of cognitive impairment has been demonstrated in lithium-treated patients.[84] The studies performed by our research group showed that the preservation, or even improvement, of cognitive functions may be connected with a quality lithium prophylaxis. This is, to a great extent, observed in excellent lithium responders, who, even after long-term lithium treatment, have normal cognitive functions when compared to healthy, matched controls.[85,86] A decrease in serum BDNF has been postulated as a marker of later stage of bipolar disorder[87] whereas excellent lithium responders, with a mean of 21 years of lithium treatment, have normal serum BDNF levels.[86]

Several mechanisms may be responsible for a favorable effect of lithium on cognitive functions in excellent lithium responders. Probably, the most important is a total prevention of affective episodes which themselves may be toxic for the brain and cause a deterioration of cognitive functions.[88,89] Second, a neurotrophic effect of lithium may play a role, with stimulation of the BDNF system, and inhibition of GSK-3β, as the main elements. Another possible mechanism could also be connected with some antiviral properties of lithium. Dickerson et al.,[90] demonstrated that infection with herpex simplex virus may be associated with cognitive deficits in bipolar disorder, whereas, in our study, long-term lithium administration was connected with attenuation, or remission, of herpes infection.[91] It is also possible that excellent lithium responders even before the treatment may constitute a subgroup of bipolar disorder with most favorable clinical course and outcome including a good status of cognitive functions.

Genome-wide Association Studies. A number of genome-wide association studies (GWAS) have been performed in recent years, some of which also focused on lithium response. In 2008, a family based association study of lithium-related candidate genes in bipolar disorder was performed, where lithium genes were selected as related primarily to inositol 1,4,5-triphosphate (17 genes), to GSK3β/Wnt signaling (39 genes) and to those implicated by mRNA expression data and related approaches (35 genes). No association with bipolar disorder was found in relation to genes specifically connected with lithium mechanisms.[92] In the same year, a paper appeared describing the results of GWAS in bipolar disorder, where the highest signal was obtained with the *DGKH* gene, which encodes a key protein in the lithium-sensitive phosphatidyl inositol pathway.[93]

American researchers utilized GWAS data, obtained from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, to examine association with risk for recurrence among patients treated with lithium, and subsequently examined the regions that showed the greatest evidence of association in a second cohort of bipolar patients drawn from a clinical population at University College, London. A phenotype definition was that of achieving euthymia for at least 8 weeks during prospective follow-up. It turned out that, of the regions with a p value of $<5 \times 10^{-4}$ in the STEP-BD cohort, five (8q22, 3p22, 11q14, 4q32, 15q26) showed consistent evidence of association in a second cohort. The authors found a region of special interest on chromosome 4q32 spanning a *GRIA2* gene, coding for the glutamate AMPA receptor.[94]

In a GWAS study performed by Squassina et al.[95] on lithium-treated Sardinian patients with bipolar disorder, phenotypic assessment of lithium response was made, using the retrospective criteria of a long-term treatment response scale. The strongest association, also supported by the quantitative trait analysis, was shown for a single nucleotide polymorphism (SNP) of the amiloride-sensitive cation channel 1 neuronal (*ACCN1*) gene, located on chromosome 17q12, encoding a cation channel with high affinity for sodium, and permeable to lithium.

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Recent GWAS study performed by the Taiwanese researchers included 294 bipolar patients of Han Chinese descent, receiving lithium treatment. The strongest association with the response to lithium was obtained with the gene coding glutamate decarboxylase-like protein 1 (GADL1), located on chromosome 3p24.[96] Glutamate decarboxylase is an enzyme that catalyzes the decarboxylation of glutamate to GABA (gamma-aminobutyric acid) that makes it an important factor for both glutamatergic and GABA-ergic neurotransmission.

Following an initiative by the International Group for the Study of Lithium-Treated Patient and the Unit on the Genetic Basis of Mood and Anxiety Disorders at the National Institute of Mental Health, lithium researchers from around the world have formed the Consortium on Lithium Genetics (ConLiGen). The aim of the ConLiGen was to establish the largest sample to date for genome-wide studies of lithium response in bipolar disorder.[97] This sample currently comprises more than 2000 patients characterized for response to lithium treatment. Such an endophenotype has been defined retrospectively by means of the Alda scale.[12] A recent article by Manchia et al.[98] reports on substantial inter-rater agreement and reliability of lithium response assessed in twenty nine ConLiGen sites. Two definitions of lithium response, one dichotomous and the other continuous were identified.

The first genetic results of the ConLiGen initiative including 1200 patients were presented during a CINP meeting in Stockholm in 2012. The GWAS top hit ($p = 1.52 \times 10^{-6}$) was found for the *SLC4A10* gene coding solute carrier family 4, sodium bicarbonate transporter, member 10, which belongs to a family of sodium-coupled bicarbonate transporters. This gene is located on chromosome 2q24 and is highly expressed in the hippocampus and cerebral cortex. It has been implicated in complex partial epilepsy and mental retardation as well as being a subject of interest in recurrent major depression. The bicarbonate sensitive pathway is the most important mechanism for active lithium influx into the cell.[99] Recently, based on 218 cases of Han Chinese or Japanese ancestry, an attempt was made to replicate the results of Chen et al.[96] However, no association was found between *GADL1* gene and lithium response in this ConLiGen sample.[100]

Genetic factors associated with lithium prophylactic efficacy in BD are summarized in Table 2.

CONCLUDING REMARKS

Lithium still remains a cornerstone for the long-term therapy of bipolar disorder, and a number of clinical and biological factors have been identified as connected with favorable prophylactic response to this ion. However, this review of clinical and genetic data connected with lithium efficacy has a number of limitations. They include relatively small samples of patients in many clinical and genetic studies as well as that some studies may have been prescreened for good outcome cases. Only a minority of results obtained in candidate gene studies has been consistently replicated and some GWAS research were not specifically aimed for lithium response. In this respect, the forthcoming GWAS results achieved within the framework of the ConLiGen project can make an important step forward.

Bearing this limitations in mind, it seems, nevertheless, that on the basis of the data provided, a clinical and psychological profile of "lithium responder" can be constructed. As to biological factors, mainly genetic ones, it may be possible that with the progress of pharmacogenomics, clinicians will eventually be assisted by a panel of genetic tests that may successfully predict which bipolar disorder patient is the most likely to have the best response to lithium.

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Notes

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