Chapter 16

Biomarkers of lithium efficacy in bipolar disorders

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16.1 Lithium's efficacy

A biomarker is a measurable indicator of some biological state or condition. In the case of lithium treatment, this is a biological marker connected with its prophylactic efficacy as well as efficacy in acute episodes of mania and depression.

As a date of the introduction of lithium into contemporary psychiatry, the paper of Australian psychiatrist, John Cade, is regarded, in which he described a favorable effect of lithium carbonate in patients with mania (Cade, 1949). Twenty years ago, in the review of 12 controlled studies, Poolsup, Li Wan Po, and de Oliveira (2000) showed a significantly better efficacy of lithium in mania, compared with placebo and similar to anticonvulsant drugs such as carbamazepine and valproates. However, in a recent *meta*-analysis of multiple antimanic medications, lithium was outperformed by both haloperidol and atypical antipsychotic drugs such as olanzapine and risperidone (Cipriani et al., 2011). Nevertheless, lithium still remains a valuable antimanic drug and lithium monotherapy is mostly indicated for patients with "euphoric" mood elevation, without irritability of mixed features, exhibiting moderate psychomotor hyperactivity. In severe mania, lithium is usually employed in combination with other antipsychotic or mood-stabilizing agents.

In the early 1960s, Geoffrey Hartigan from Great Britain first demonstrated that 3-year lithium administration prevents both manic and depressive episodes in bipolar and unipolar affective illness (Hartigan, 1963). This was followed by a similar article from Denmark (Baastrup, 1964). Several years later, a confirmatory Danish study demonstrated such effect was on a larger group of patients (Baastrup & Schou, 1967). Three *meta*-analyses of the 21st century have amply confirmed the prophylactic effectiveness of lithium in bipolar disorder (Geddes, Burgess, Kawton, Jamison, & Goodwin, 2004;

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Nivoli, Murru, & Vieta, 2010; Severus et al., 2014). Nowadays, lithium is regarded as the drug of the first choice for long-term prevention of mood recurrences in bipolar disorders. There have also been promising results with using lithium for prophylactic purposes in recurrent depression (Souza & Goodwin, 1991; Undurraga et al., 2019).

Antidepressant effects of lithium were revealed in the 1970s (Mendels, 1976; Rybakowski, Chłopocka, Lisowska, & Czerwiński, 1974). It was suggested that such therapeutic results may be stronger in bipolar than unipolar depression although generally weaker than tricyclic antidepressants. In the early 1980s, the augmentation of the efficacy of antidepressants by lithium was first demonstrated (De Montigny, Grunberg, Mayer, & Deschenes, 1981). Rybakowski and Matkowski (1992) showed that the augmenting effect of lithium is better in depression in the course of bipolar disorder than in recurrent depression. A review on this subject, in particular, research comparing the effect of lithium with placebo was performed by the German psychiatrists. They showed the effectiveness of lithium augmentation of antidepressants in treatment-resistant depression both in the course of bipolar disorder and recurrent depression, with a response in more than half of depressed patients (Crossley & Bauer, 2007). In current therapeutic guidelines, the potentiation of antidepressants by lithium in treatment-resistant depression has been frequently advocated.

In this chapter, the most important neurobiological markers of the efficacy of lithium prophylaxis, lithium treatment of acute episodes of mania and depression, and lithium augmentation of antidepressants will be presented and discussed. They also accommodate the data of the recent article aimed to cover the papers on this topic published between 1990 and December 22, 2017 (Fornaro et al., 2018).

16.2 Biomarkers of lithium prophylaxis efficacy

The introduction by the Canadian psychiatrist, Grof (1999) the term "excellent lithium responders" made an important step for a clinical description of patients responding to lithium prophylaxis. Grof gave such a name to subjects who on monotherapy with lithium experienced a dramatic change in their life as their mood episodes were completely prevented. We followed up 60 patients who started lithium prophylaxis in the 1970s, and 49 patients beginning this procedure in the 1980s for 10 years. Those without mood episodes during this period made 35% of the first group and 27% of the second one, roughly one-third of bipolar subjects treated longitudinally with lithium (Rybakowski, Chłopocka-Woźniak, & Suwalska, 2001). According to Grof (2010), excellent lithium responders have a moderate number of episodes, euthymic remission periods, no other psychiatric comorbidity, and often a family history of bipolar disorder. These features may be similar to the "manisch-depressives Irresein," described by Emil Kraepelin (1899).

Following this, many clinical markers of lithium prophylactic efficacy were identified (Rybakowski, 2020).

However, given a plethora of clinical markers of lithium prophylactic efficacy, the distinct biochemical biomarkers of such efficacy have been scarce. One was proposed by Frye et al. (2009) who showed that increased serum thyroid-stimulating hormone (TSH) was associated with a higher probability of depressive relapse in bipolar patients receiving lithium maintenance treatment. In very good lithium responders experiencing total disappearance of mood recurrences, the progression of the illness can be arrested. Kauer-Sant'Anna et al. (2009) postulated that a decline in serum brain-derived neurotrophic factor (BDNF) may serve as an indicator of the later period of bipolar disorder. In contrast to this, we have demonstrated that in excellent lithium responders having an average of 21 years of lithium prophylaxis, serum BDNF levels were comparable to normal controls (Rybakowski & Suwalska, 2010). In another study, it was found that in bipolar patients on prophylactic lithium with long-term remission, the concentrations of inflammatory cytokines were similar to those of healthy subjects (Remlinger-Molenda, Wojciak, Michalak, Karczewski, & Rybakowski, 2012).

In recent years, a hope for biological markers of lithium prophylactic efficacy has been brought about by research performed on the induced pluripotent stem cells (iPSCs). These investigations showed the differences between such cells obtained from lithium responders versus nonresponders. In two of these iPSC models, the differences between these two groups lied in influencing hyperexcitability by cells obtained from responders, in contrast to nonresponders. Mertens et al. (2015) investigated the cellular phenotypes of hippocampal dentate gyrus-like neurons derived from iPCSs of patients with bipolar disorder. The hyperexcitability phenotype of young neurons was selectively reversed by lithium treatment only in neurons derived from lithium-responding patients. Similarly, Stern et al. (2018) using iPSCs derived from Epstein–Barr virus immortalized B-lymphocytes showed that chronic lithium treatment reduced the hyperexcitability of these cells in lithium responders but not in lithium nonresponders. In another study using iPSCs, Tobe et al. (2017) showed that lithium alters the phosphorylation state of collapsin response mediator protein-2 (CRMP2). The ratio of phosphorylated CRMP2 (pCRMP2) to CRMP2 was significantly higher in lithium responders than in nonresponders.

Recently, an attempt to relate lithium efficacy to its effect on chronotype and circadian rhythms has also been made. In our study we found that lithium treatment is connected with a tendency to morning chronotype (Dopierała, Chrobak, Tereszko, & Rybakowski, 2017). McCarthy et al. (2019) examined morning versus evening preference (chronotype) as a dimension of circadian rhythm function in lithium responders and nonresponders and in a subset of patients measured circadian rhythms in skin fibroblasts longitudinally over 5 days using a bioluminescent reporter. They

found that lithium responders showed a difference in chronotype, with higher levels of morningness. Scott, Hennion, Meyrel, Bellivier, and Etain (2020) demonstrated a difference between lithium responders and nonresponders in circadian rest−activity markers obtained in actigraphy studies.

The quality of prophylactic lithium response makes an attractive topic for molecular genetic studies. They have brought about multiple genetic biomarkers connected with long-term lithium efficacy. Up to the second decade of the 21st century, they have been dominated by the strategy of the "candidate gene." In this approach, a specific gene based on its function is tested for possible involvement in the pathogenesis of disease or mechanism of pharmacological treatment. Genetic markers of known function or located in potentially important regulatory gene regions are analyzed in case-control studies to determine if the variant is involved in disease or pharmacological treatment of it. A review of molecular genetic studies employing the method of the candidate gene was made by the author of this article 7 years ago. Associated with prophylactic lithium response were the polymorphisms of genes for neurotransmission − serotonin transporter, dopamine D1 receptor (DRD1) genes, second messengers (inositol polyphosphate 1-phosphatase, CREB1 genes), glycogen synthase kinase 3β (GSK-3β) gene, BDNF gene, glucocorticoid receptor (NR3C1) gene, circadian rhythms (Rev-Erba-α) gene, and the genes located on chromosome 22q11−13 such as breakpoint cluster region (BCR), X-box binding protein 1 (XBP1), and the calcium channel gamma-2 subunit (CACNG2) genes (Rybakowski, 2013).

Following this article, the candidate gene studies, although dominated by other methods, especially genome-wide association studies (GWAS), brought about some new findings. In Poznan study, an association between prophylactic lithium efficacy and three polymorphisms (rs1360780, rs7748266, and rs9296158) of the FKBP5 gene, one of the main genes involved in the hypothalamic−pituitary−adrenal axis function was demonstrated (Szczepankiewicz et al., 2018), adding to our previous results on the glucocorticoid receptor (NR3C1) gene (Szczepankiewicz, Rybakowski, Suwalska, & Hauser, 2011). Chen et al. (2016) suggested an association of the polymorphism of the glutamate decarboxylase-like protein (GADL1) gene with the efficacy of lithium maintenance in the Han Chinese population with bipolar disorder. Miranda et al. (2019) in a study of 45 candidate genes confirmed an association of the CACNG2 gene with lithium prophylactic response, also suggesting a role of the neuregulin (NRG1) gene in this respect. Recently, Iranian investigators revealed an association of lithium prophylactic efficacy with a polymorphism of the adenylate cyclase 2 (ADCY2) gene (Afjeh et al., 2020). Two studies assessed the polymorphisms of so-called "clock" genes in connection with prophylactic lithium response. In the first study, the association with the efficacy of lithium prophylaxis was demonstrated for six single-nucleotide polymorphisms (SNPs) and three haplotype blocks of the aryl hydrocarbon receptor nuclear translocator-like

(ARNTL) gene, and two SNPs and one haplotype block of the timeless circadian clock (TIM) gene (Rybakowski, Dmitrzak-Weglarz, Kliwicki, & Hauser, 2014). In the second study, the RAR-related orphan receptor-a gene (RORA) and the peroxisome proliferator-activated receptor-gamma, coactivator 1 alpha gene (PPARGC1A or PGC-1α) were significantly associated with lithium response (Geoffroy et al., 2016).

Some research of candidate genes were also performed using lymphoblastoid cell lines obtained from lithium responders versus nonresponders. In this respect, Milanesi et al. (2015) showed an association with lithium prophylactic response of the insulin-like growth factor 1 (IGF-1) gene, while Moreira et al. (2017) did not confirm an association of the GADL1 gene in Caucasian patients with bipolar disorder.

In 2009, an initiative of the National Institute of Mental Health and the International Group for the Study of Lithium-treated Patients resulted in the formation of the International Consortium on Lithium Genetics (ConLiGen), aiming for the first GWAS of lithium response (Schulze et al., 2010). In 2013, a report of the key phenotypic measures of the "Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder" scale, known as the Alda's scale, used by ConLiGen was presented (Manchia et al., 2013). In the first GWAS of prophylactic lithium efficacy, 2500 subjects participated from 22 sites. The criteria for association with lithium response were satisfied by a single locus of four linked SNPs located on chromosome 21. This locus has two genes for long, noncoding RNAs (lncRNAs) managing central nervous system gene expression (Hou et al., 2016).

A subsequent paper from the ConLiGen group showed that polygenic score for schizophrenia determines the worse response to lithium (International Consortium on Lithium Genetics ConLi + Gen et al., 2018) which may correspond with our study on the negative association of prophylactic lithium effect with a predisposition to psychotic symptoms (Dembińska-Krajewska, Kliwicki, Chłopocka-Woźniak, & Rybakowski, 2012). Amare et al. (2020) showed that the polygenic score for major depression is also negatively correlated with lithium response in bipolar patients. Recently, the ConLiGen group studied an association of lithium response with human leukocyte antigen (HLA) variants showing that good response to lithium was associated with HLA-mediated low inflammation while the poor response was connected with an inflammatory status (Le Clerc et al., 2020).

Several genes were identified from GWASs performed outside the ConLiGen group. Higgins, Allyn-Feuer, Barbour, and Athey (2015) analyzing the results of GWAS studies found a significant association with the lithium response of the glutamate receptor AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) 2 gene network. Song et al. (2016) in their *meta*-analyses of Swedish and UK samples obtained an association with lithium response of the SNP (rs116323614) of the cytosolic protein (SEC14)

and spectrin domains 1 (SESTD1) gene encoding a protein involved in the regulation of phospholipids. Sardinian investigators applied an integrated analytical approach using genome-wide expression and genotyping data from lithium responsive and lithium nonresponsive bipolar patients identified the zinc finger protein 429 (ZNF429) gene, as involved in modulating lithium efficacy (Pisanu et al., 2018).

Two papers investigated the contribution of micro-RNA (miR) to lithium prophylactic efficacy. The ConLiGen group showed an association of the miR-630 with continuous trait and the miR-607 with the dichotomous phenotype of lithium response (Reinbold et al., 2018). In the second study, Pisanu et al. (2019) performing next-generation sequencing to measure genome-wide miR expression in lymphoblastoid cell lines and integrating with microarray genome-wide expression data identified the miR-320a and miR-155−3p involved in lithium response.

The lymphoblastoid cell lines obtained from lithium responders and nonresponders, already mentioned, made an important tool for identifying biomarkers of the prophylactic lithium effect. The results of RNA sequencing gene expression in lymphoblastoid cell lines were presented by Breen et al. (2016). In this paper, several networks connected with lithium response included apoptosis and defense response pathways, protein processing, response to endoplasmic reticulum stress, and also a signature similar to that observed with clonidine treatment. Individual gene markers were involved in processes of cell cycle and nucleotide excision repair. Papadima et al. (2018) using microarray expression data of lymphoblastoid cell lines RNA showed that higher levels of the binding motif protein 3 (RBM3) gene are connected with lithium response. Recently Milanesi et al. (2019) performing RNA sequencing of lymphoblastoid cell lines identified two other genes associated with lithium prophylactic efficacy such as hepatoma-derived growth factor, related protein 3 (HDGFRP3) gene, and DNA-binding protein inhibitor ID-2 (ID2) gene.

Three other investigations should be mentioned employing diverse molecular genetic methods. Transcriptomic profiling using the whole blood-derived RNA sequence data demonstrated association with lithium prophylactic efficacy of the genes connected with the mitochondrial functioning such as electron transport chain (ETC) and oxidative phosphorylation (OXPHOS) (Stacey et al., 2018). Jacobs et al. (2020) investigated whole-exome sequencing (WES) of twins having a discordant response to lithium and a distinct course of illness. Using this method, six genes of particular interest emerged such as neurofibromin type 1 (NF1), biorientation of chromosomes in cell division 1 (BOD1), Golgi-associated gamma adaptin ear-containing ARF binding protein 3 (GGA3), disrupted in schizophrenia 1 (DISC1), neuromedin U receptor 2 (NMUR2), and Huntingtin-interacting protein 1 related (HIP1R). French investigators examined whether the prophylactic response to lithium in type bipolar patients can be associated with

distinct blood DNA methylation profiles. The DNA samples from 15 excellent responders and 11 nonresponders were compared. The targeted enrichment followed by high-resolution next-generation sequencing identified differentially methylated regions (DMRs) with good discriminatory power for the response to lithium. The genes associated with these DMRs included eukaryotic translation initiation factor 2B subunit epsilon (*EIF2B5*), von Willebrand factor A domain containing 5B2 (*VWA5B2*), and ral GTPase activating protein catalytic alpha subunit 1 (*RALGAPA1*) suggesting that biomarkers of lithium prophylactic response can be also identified through peripheral epigenetic measures (Marie-Claire et al., 2020).

The summary of biomarkers connected with lithium prophylactic efficacy is presented in Table 16.1.

16.3 Biomarkers for lithium efficacy in acute mood episodes

The interest for biomarkers of lithium efficacy in acute mood episodes is much lower than this concerning the long-term treatment. However, quite a few studies in this respect have been performed, identifying several markers of such efficacy.

The concentration of lithium for the treatment of manic episodes should be in the range of 0.8−1.2 mmol/L which is higher than for prophylactic purposes. However, no formal study was performed showing a connection of antimanic response to lithium with higher serum lithium concentration. On the other hand, Kato, Inubushi, and Takahashi (2007) described a correlation between brain lithium concentration measured by lithium-7 magnetic resonance spectroscopy (^{7}Li MRS) and improvement of mania in a 4-week study.

In the search for neuroimaging markers of lithium efficacy in mania, Fleck et al. (2017) developed a design called LITHium Intelligent Agent (LITHIA) as a machine learning system integrating data from functional magnetic resonance imaging (fMRI) and proton magnetic resonance spectroscopy (^{1}H-MRS). They found that in first-episode mania, the system was able to predict with more than 80% accuracy the posttreatment symptom reduction at 8 weeks.

The studies for biological markers of lithium efficacy in mania started more than 30 years ago when Swann et al. (1987) showed that nonresponders had a greater reduction of 3-methoxy-4-hydroxyphenylglycol (MHPG) in cerebrospinal fluid and greater urinary excretion of MHPG. More recently De Sousa et al. (2011) showed in lithium responders in mania a significant increase in plasma BDNF levels and Li et al. (2015) demonstrated in good responders a decrease in plasma level of tumor necrosis factor-alpha (TNF-α), tumor growth factor beta1 (TNF-β1), interleukin-23 (IL-23), and IL-17.

Treatment of bipolar depression with lithium monotherapy has not been frequently used in recent years. However, there have been some studies of

TABLE 16.1 **Biomarkers connected with lithium's prophylactic efficacy in bipolar disorder.**

Author (s)/ (year)	Method	Biomarker	Outcome
Frye et al. (2009)	Assessment of depressive relapses	TSH	Higher TSH connected with a higher probability of depressive relapse
Rybakowski and Suwalska (2010)	Clinical assessment of lithium response	BDNF	Excellent lithium responders have higher serum BDNF than the remaining patients
Remlinger-Molenda et al. (2012)	Clinical assessment of lithium response	IL-1β, IL-2, IL-6, IL-10, TNF-α, IFN-γ	In good lithium responders, the normal level of these cytokines
Mertens et al. (2015)	iPSC	Hyperexcitability of dentate gyrus-like neurons	Hyperexcitability reversed by lithium responders and not by nonresponders
Stern et al. (2018)	iPSC	Hyperexcitability of immortalized B-leukocytes	Hyperexcitability reversed by lithium responders and not by nonresponders
Tobe et al. (2017)	iPSC	The phosphorylation state of CRMP2	The ratio of phosphorylated CRMP2/CRMP2 higher in lithium responders
McCarthy et al. (2019)	Assessment of chronotype and circadian rhythms	Morning vs evening chronotype	Lithium responders have higher level of morningness
Scott et al. (2020)	Actigraphy	Rest–activity markers	Lithium responders have more stable circadian rhythmicity
Rybakowski (2013)	Summary of candidate gene studies performed until 2013	5-HTTPRL DRD1 IPP1 CREB1 GSK-3β BDNF NR3C1 Re-Erba-α RBC XBP1 CACNG2	Association of the polymorphism of these genes with prophylactic lithium response

(*Continued*)

TABLE 16.1 (Continued)

Author (s)/ (year)	Method	Biomarker	Outcome
Szczepankiewicz et al. (2018)	Clinical assessment of lithium response	FKBP5	Association of three FKBP5 polymorphisms with prophylactic lithium response
Chen et al. (2016)	Clinical assessment of lithium response	GADL1	Association of GADL1 gene polymorphism with lithium response
Miranda et al. (2019)	Clinical assessment of lithium response	CACNG2 NRG1	Association of CACNG2 and NRG1polymorphism with lithium response
Afjeh et al. (2020)	Clinical assessment of lithium response	ADCY2	Association of ADCY2 gene polymorphism with lithium response
Rybakowski et al. (2014)	Clinical assessment of lithium response	Clock genes ARNTL TIM	Association of ARNTL and TIM polymorphisms with lithium response
Geoffroy et al. (2016)	Clinical assessment of lithium response	Clock genes RORA PGC-1α	Association of RORA and PGC-1α polymorphism with lithium response
Milanesi et al. (2019)	Lymphoblastoid cell lines	IGF-1	Exogenous IGF-1 increased Li sensitivity in responders
Hou et al. (2016)	GWAS – ConLiGen Clinical assessment of lithium response	Genes lncRNAs AL157359.3 AL157359.4	Genes on chromosome 21 in response linked region
International Consortium on Lithium Genetics ConLi + Gen et al. (2018)	GWAS – ConLiGen Clinical assessment of lithium response	The polygenic score for schizophrenia	The polygenic score for schizophrenia connected with worse response

(*Continued*)

TABLE 16.1 (Continued)

Author (s)/ (year)	Method	Biomarker	Outcome
Amare et al. (2020)	GWAS – ConLiGen Clinical assessment of lithium response	The polygenic score for major depression	The polygenic score for major depression connected with worse response
LeClerc et al. (2020)	GWAS – ConLiGen Clinical assessment of lithium response	HLA variants	Good response – HLA-mediated low inflammation poor response – inflammatory status
Higgins et al. (2015)	GWAS Clinical assessment of lithium response	AMPA2	Association of AMPA2 gene network with lithium response
Song et al. (2016)	GWAS Clinical assessment of lithium response	SESTD1	Association of SESTD1 gene polymorphism with lithium response
Pisanu et al. (2018)	GWAS Clinical assessment of lithium response	ZNF429	Association of ZNF429 gene polymorphism with lithium response
Reinbold et al. (2018)	GWAS – ConLiGen Clinical assessment of lithium response	micro-RNA: miR-630 miR-607	Association of miR-630 with continuous trait and miR-607 with the dichotomous phenotype of Li response
Pisanu et al. (2019)	Genome-wide miRNA expression in lymphoblastoid cell lines	miR-320a miR-155−3p	MiR-320a and miR-155−3p involved in lithium response
Breen et al. (2016)	RNA gene sequencing in lymphoblastoid cell lines	Gene networks: Apoptosis Defense response Protein process Reticulum stress Clonidine Cell cycle Nucleotide repair	All the networks connected with lithium response

(*Continued*)

TABLE 16.1 (Continued)

Author (s)/ (year)	Method	Biomarker	Outcome
Papadima et al. (2018)	Microarray RNA expression in lymphoblastoid cell lines	RBM3	Higher levels of RBM3 gene associated with lithium response
Milanesi et al. (2019)	RNA gene sequencing in lymphoblastoid cell lines	HDGFRP3 ID-2	HDGFRP3 and ID-2 genes associated with lithium response
Stacey et al. (2018)	Transcriptomic profiling of whole blood RNA-sequence	Genes of mitochondrial functioning ETC, OXPHOS	ETC and OXPHOS genes connected with Li response
Jacobs et al. (2020)	Whole-genome sequencing of monozygotic twins with a discordant response to lithium	NF1 BOD1 GGA3 DISC1 NMUR2 HIP1R	Genes of different expression in monozygotic twins with a discordant response to lithium
Marie-Claire et al. (2020)	Blood DNA methylation profiles in DNA samples of lithium responders and nonresponders	EIF2B VWA5B2 RALGAPA1	Genes with differentially methylated regions in lithium responders and nonresponders

Abbreviations: *TSH*, thyroid-stimulating hormone; *BDNF*, brain-derived neurotrophic factor; *iPSC*, induced pluripotent stem cell; *TNF*, tumor necrosis factor; *IL*, interleukin; *IFN*, interferon; *CRMP2*, collapsin response mediator protein-2; *ADCY2*, adenylate cyclase 2; *ARNTL*, aryl hydrocarbon receptor nuclear translocator-like; *TIM*, timeless circadian clock; *RORA*, RAR-related orphan receptor-a gene; *IGF-1*, insulin-like growth factor 1; *GWAS*, genome-wide association studies; *HLA*, human leukocyte antigen; *HDGFRP3*, hepatoma-derived growth factor, related protein 3; *ETC*, electron transport chain; *OXPHOS*, oxidative phosphorylation; *NF1*, neurofibromin type 1; *BOD1*, biorientation of chromosomes in cell division 1; *GGA3*, Golgi-associated gamma adaptin ear-containing ARF binding protein 3; *DISC1*, disrupted in schizophrenia 1; *NMUR2*, neuromedin U receptor 2; *HIP1R*, Huntingtin-interacting protein 1 related; *EIF2B*, eukaryotic translation initiation factor 2B; *VWA5B2*, von Willebrand factor A domain containing 5B2; *RALGAPA1*, ral GTPase activating protein catalytic alpha subunit 1; *SESTD1*, SEC14 and spectrin domains 1; *ZNF429*, zinc finger protein 429.

biological markers related to the results of such treatment. In lithium responders, they revealed higher pretreatment levels of leptin (Soeiro-de-Souza et al., 2014), and lower levels of thiobarbituric acid reactive substance (TBARS) after lithium treatment (De Sousa et al., 2014).

Given the increasing occurrence of treatment-resistant depression, a strategy of adding lithium to antidepressants can be now considered as an important indication for lithium use. This applies to depression in both unipolar and bipolar mood disorder. Lithium can be safely added to various kinds of antidepressants (tricyclic, selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors - (SNRI)) and the concentration should be attained of 0.6−0.8 mmol/L. In about one-fourth of patients, a rapid response (within several days) is observed. As to clinical factors associated with a better effect, higher intensity of depression, serious loss of weight, psychomotor slowing, frequent previous depressive episodes, and a familial occurrence of depression have been suggested (Bauer, Adli, Ricken, Severus, & Pilhatsch, 2014).

There have been some molecular genetic studies connected with the efficacy of lithium augmentation of antidepressants. In the first study, Adli et al. (2007) showed that the effect of lithium augmentation can be associated with the −50T/C SNP of the GSK-3β gene. Their results showing better efficacy of lithium augmentation in the carriers of the C allele of this polymorphism concur with studies showing the same allelic effect for the efficacy of lithium prophylaxis (Benedetti et al., 2005). On the other hand, Stamm et al. (2008) showed that the s/s genotype of the serotonin transporter 5-HTTLPR gene polymorphism was associated with the better augmentation effect of lithium. Interestingly, this genotype was connected with worse response to antidepressants (Smeraldi et al., 1998), and to lithium prophylactic effect (Rybakowski et al., 2005) what may point to some specificity of this polymorphism as far as various therapeutic effects of lithium are concerned. Recently, Bopp et al. (2019) showed that two polymorphisms of the leptin gene are associated with weight gain during lithium augmentation in major depression.

As to biochemical biomarkers, De Montigny et al. (1981) who first described lithium augmentation of antidepressants suggested a stimulation by lithium of the serotonergic system. This may correspond to the study of German authors showing in responders to lithium augmentation, a decrease of ghrelin, a peptide inhibiting serotonin secretion (Ricken et al., 2017). In another study of these authors, the positive outcome of lithium augmentation was connected with an increase of BDNF plasma levels (Ricken et al., 2013).

The summary of biomarkers connected with lithium efficacy in acute episodes and augmentation of antidepressants is presented in Table 16.2.

TABLE 16.2 Biomarkers connected with lithium efficacy in acute mood episodes and treatment-resistant depression.

Author (s)/(year)	Aim of the study	Biomarker	Outcome
Kato et al. (2007)	Treatment response in mania	Li concentration in the brain measured by ^{7}Li MRS	Treatment response correlated with Li brain concentration
Fleck et al. (2017)	Treatment response first-episode mania	Machine learning of the LITHIA system	Data of fMRI and ^{1}H-MRS predicted response at 8 weeks
Swann et al. (1987)	Treatment response in mania	MHPG	Nonresponders: Reduction in CSF > Urinary excretion
De Sousa et al. (2011)	Treatment response in mania	BDNF	Responders: > Plasma BDNF
Li et al. (2015)	Treatment response in mania	TNF-α, TNF-β1 IL-23, IL-17	Responders: < TNF-α, TNF-β1 < IL-23, IL-17
Soeiro-de-Souza et al. (2014)	Treatment response in depression	Leptin	Responders: > Pretreatment level
De Sousa et al. (2014)	Treatment response in depression	TBARS	Responders: < Posttreatment level
Adli et al. (2007)	Augmentation of antidepressants	GSK-3β	Better response in carriers of C allele of −50T/C SNP
Stamm et al. (2008)	Augmentation of antidepressants	5-HTTLPR	Better response in carriers of the s allele of l/s polymorphism
Bopp et al. (2019)	Augmentation of antidepressants	Leptin gene	Two polymorphisms of the leptin gene associated with weight gain
Ricken et al. (2017)	Augmentation of antidepressants	Ghrelin (a peptide inhibiting serotonin)	Responders: < Ghrelin
Ricken et al. (2013)	Augmentation of antidepressants	BDNF	Responders: > Plasma BDNF

Abbreviations: *^{7}Li MRS*, lithium-7 magnetic resonance spectroscopy; *LITHIA*, LITHium Intelligent Agent; *fMRI*, functional magnetic resonance imaging; *^{1}H-MRS*, proton magnetic resonance spectroscopy; *MHPG*, 3-methoxy-4-hydroxyphenylglycol; *CSF*, cerebrospinal fluid; *BDNF*, brain-derived neurotrophic factor; *TNF*, tumor necrosis factor; *IL*, interleukin; *TBARS*, thiobarbituric acid reactive substance; *GSK-3β*, glycogen synthase kinase 3β.

16.4 Conclusions

Currently, lithium is a drug of choice as a mood stabilizer for the maintenance treatment of bipolar disorder. In addition to the features of "excellent lithium responders," many other clinical and biological markers connected with favorable response to lithium prophylaxis have been identified. The biomarkers were obtained by manifold methods, including biochemistry, lymphoblastoid cell lines, iPSCs, and diverse kinds of genetic analyses. The employment of genetic methods made it possible to identify multiple genes connected with prophylactic lithium response. All these biomarkers point to complex biological mechanisms underlying the lithium prophylactic effect. A question arises whether some of these biomarkers or a cluster of them could have a practical application such as to estimate a probability of good lithium response in the early phase of lithium prophylaxis. In our study of the interaction between polymorphisms of BDNF and 5-HTTLPR genes, we found that some combinations of them are connected with very good and some with poor response to prophylaxis (Rybakowski et al., 2007). Many other biomarkers, both genetic and nongenetic could be added to known clinical factors to better estimate a probability of lithium response.

Lithium has also obtained its place in the treatment of an acute episode of mania and bipolar depression and, especially, the augmentation of antidepressants in treatment-resistant depression. Several biological markers of lithium's efficacy in these conditions have been obtained. A practical application of these biomarkers would be especially helpful in the case of treatment-resistant depression. For example, from molecular genetic studies performed by German investigators, it emerges that the carriers of C allele of −50T/C SNP of the GSK3B gene and those of s allele of the s/l 5-HTTLPR polymorphism may expect the best effect of lithium in this respect. Again, this finding along with known clinical factors can be used to better estimate a probability of lithium response.

In conclusion, a search for biomarkers of lithium efficacy, seems to be greatly substantiated. It can help to identify the best candidates for various modalities of lithium administration in the vein of the personalized medicine.

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