

Predictors of lithium response in bipolar disorder

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Abstract: While lithium is generally regarded as the first-line agent for patients with bipolar disorder, it does not work for everyone, which raises the question: can we predict who will be most likely to respond? In this paper, we review the most compelling clinical, biologic, and genetic predictors of lithium response in bipolar disorder. 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, and a later age at onset of bipolar disorder. While several biologic predictors have been studied, the results are preliminary and require replication with studies of larger patient samples over longer observation periods. Neuroimaging is a particularly promising method given that it might concurrently illuminate pathophysiologic underpinnings of bipolar disorder, the mechanism of action of lithium, and potential predictors of lithium response. The first genome-wide association study of lithium response was recently completed. No definitive results emerged, perhaps because the study was underpowered. With major new initiatives in progress aiming to identify genes and genetic variations associated with lithium response, there is much reason to be hopeful that clinically useful information might be generated within the next several years. This could ultimately translate into tests that could guide the choice of mood-stabilizing medication for patients. In addition, it might facilitate pharmacologic research aimed at developing newer, more effective medications that might act more quickly and yield fewer side effects.

Keywords: bipolar disorder, genetics, lithium, neuroimaging, predicting response

Bipolar disorder

Bipolar disorder (BP), formerly called manic–depressive illness, is a mood disorder characterized by two poles of mood, mania and depression. With a lifetime prevalence of 1.3–3.1% of the population [Merikangas *et al.* 2007], BP places those affected at risk for episodes at the two poles, but also for hypomanic and mixed mood episodes. There are two types of BP, BP I and BP II, based on current diagnostic criteria as described in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). Mania serves as the clinical feature that distinguishes not only BP from major depression (sometimes called unipolar depression), but also BP I from BP II. That is, the presence of at least one lifetime episode of mania warrants a diagnosis of BP I. In BP II, patients have hypomania, a milder form of mania. While patients typically

experience depressive episodes in both forms of BP, a lifetime history of clinical depression is not required for the diagnosis of BP I. The goal of this section is to review the clinical features of BP.

Mania is characterized by elated to irritable mood, increased activity, inflated sense of self worth, racing thoughts, diminished sleep requirement, distractibility, and pressured speech. Psychotic symptoms, such as grandiose delusions or auditory hallucinations, are not uncommon in BP, particularly in the manic phase [Potash *et al.* 2001]. Another sign of mania is impaired judgment, which may lead to uncharacteristic behaviors such as spending sprees or promiscuous sexual activity. By contrast, hypomanic episodes are milder versions of manic ones, with no psychotic symptoms, and less impairment, or sometimes none at all. Further, mood symptoms

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must persist for at least 4 days in hypomania, as opposed to a full week in mania.

During the depressive phase of BP, patients typically develop a low, sad, or apathetic mood, physical exhaustion, changes in appetite, impaired concentration, decreased hedonic capacity, and insomnia. Another cardinal symptom of clinical depression is the presence of a diminished sense of self worth or feelings of guilt. Hopelessness frequently ensues, which may lead to thoughts of death or suicide. In a depressive episode, symptoms are present for at least 2 weeks and lead to significant impairment in functioning.

Mixed states arise when manic and depressive symptoms are present at the same time. To meet current diagnostic criteria for a mixed episode, patients must demonstrate full criteria for mania and major depression for at least 1 week. While few patients meet this very high diagnostic threshold, many experts believe that clinically important mixed states not meeting these criteria occur fairly commonly.

BP is associated with many costs, the most alarming of these being the drastically elevated suicide rate seen in the illness, with the risk being around 20-fold greater in those with BP compared with the general population [Osby *et al.* 2001]. Further, the problems with cognition, motivation, and impulse control often lead to significant impairment in the workplace, as well as at home and in interpersonal relationships. According to the World Health Organization, BP is the sixth leading cause of disability among all diseases worldwide [Lopez and Murray, 1998].

Given the significant morbidity and mortality associated with BP, timely diagnosis and initiation of appropriate medication therapy is highly desirable. Although no cure is currently available, BP can be managed effectively using a variety of pharmacologic and psychotherapeutic treatments. The mainstay of pharmacologic treatment for BP is the class of medications known as mood stabilizers. These are agents that have been shown to be beneficial in the treatment of acute episodes and in the prevention of recurrence of bipolar illness. There are four mood stabilizers for which substantial evidence of efficacy exists: lithium, valproate, carbamazepine, and lamotrigine, with lithium being the one for which the body of supporting data is most substantial.

Neuroleptic agents, such as olanzapine, also have mood-stabilizing qualities. In addition to its use as a mood stabilizer, lithium has been shown to be an effective augmenting agent in the treatment of unipolar major depression [Crossley and Bauer, 2007].

Lithium is generally regarded as the first-line agent for the management of BP, although it does not work for everyone. For instance, Geddes and colleagues performed a meta-analysis of five randomized controlled trials comparing prophylactic lithium therapy with placebo in BP and found that lithium is more effective than placebo in preventing recurrence of illness, with 60% in the lithium group remaining well over 1–2 years compared with 40% in the placebo group [Geddes *et al.* 2004]. A meta-analysis of six studies of lithium in the treatment of acute mania found that 47% of patients responded compared with 32% of controls [Yildiz *et al.* 2011].

The results cited above raise the question: can we predict who will be most likely to respond? This type of question is one that is being asked throughout psychiatry and other clinical fields in the context of the quest for personalized medicine. One can ask the question with a focus on clinical and demographic factors, though in recent years, such research has been centered on patient-specific molecular and genetic factors that might predict which treatment(s) are expected to provide the best clinical outcomes for a given patient with a particular illness [de Leon, 2009]. After a brief review of the history of lithium as a treatment for BP, we will review the most compelling clinical, biologic, and genetic predictors of lithium response in BP with an overarching aim of advancing personalized medicine within the field of psychiatry. Table 1 provides an overview of the results of our review of these potential predictors.

The history of lithium use in bipolar disorder

Lithium has been used for the treatment of medical and psychiatric conditions such as gout, seizures, mania, and ‘general nervousness’ since the mid 1800s. However, its modern introduction into psychiatry began in 1949, when Australian psychiatrist John Cade successfully used the drug in the treatment of 10 patients with mania. Several of these patients were able to be discharged from a chronic mental hospital despite years of psychiatric instability [Cade, 1949].

Table 1. Level of support for the clinical, biologic, and genetic predictors of lithium response in bipolar disorder.

Variables	Level of support
Clinical variables	
Course of illness	+++
Family history of BP	++
Family history of Li response	++
Age of BP onset	+++
Number of BP hospitalizations	+++
Classic BP symptomatology	+
Biologic variables	
Normal EEG	+
ERPs	+
Brain imaging	+
Genetic variables	
Single-gene association studies	+
Genome-wide association study	++

BP, bipolar disorder; EEG, electroencephalography; ERP, event-related potential; Li, lithium; +, weak evidence; ++, moderate evidence; +++, strong evidence.

These findings spurred research resulting in a plethora of papers about various biologic aspects of lithium [Schou, 1999]. In 1954, Schou and colleagues performed the first randomized controlled trial of lithium in which he showed the treatment was effective and an alternative to electroconvulsive therapy (ECT) in the treatment of mania [Schou *et al.* 1954]. In the ensuing decade, a number of publications supported Schou and colleagues' findings that lithium is a successful antimanic agent.

It was not until 1967 that Baastrup and Schou systematically demonstrated that lithium confers protection against the recurrence of illness using a nonblinded mirror design in 88 women [Baastrup and Schou, 1967]. In this study, the authors demonstrated that lithium not only reduced the frequency of relapses, but also shortened the length of relapses that occurred on the medication. Baastrup and colleagues followed up with a double-blind discontinuation study of the prophylactic qualities of lithium [Baastrup *et al.* 1970]. Among the 45 patients treated with lithium, none had recurrences of their mood illness, while 21 of 39 patients treated with placebo experienced a relapse. Subsequently, the efficacy of lithium as a long-term prophylactic agent for the treatment of BP was corroborated by a series of double-blind trials conducted in the 1970s and 1980s [Grof and Muller-Oerlinghausen, 2009].

Despite its well established antimanic and prophylactic qualities, lithium became the focus of close scrutiny in the 1990s. For example, there has been concern that the prophylactic efficacy of lithium dissipates over time. In their review, Grof and Muller-Oerlinghausen offered a series of compelling arguments in favor of the mood-stabilizing properties of lithium [Grof and Muller-Oerlinghausen, 2009]. The authors asserted that the efficacy of lithium was rigorously proven using a variety of study designs including randomized, double-blind; double-blind discontinuation; and double-blind cross-over trials. Further, they argued, these older studies were not influenced by the pharmaceutical industry, a powerful force, more recently, in promoting newer mood-stabilizing medications.

Predictors of lithium response: clinical epidemiology

Since the late 1960s, a vast number of studies have investigated various clinical factors that might predict lithium response in patients with BP. In their 2005 review paper, Kleindienst and colleagues identified nearly 2000 articles published from 1966 to 2003 on this topic [Kleindienst *et al.* 2005]. In Table 2 we have summarized some of the most important of these papers. Although dozens of clinical features have been examined as potential predictors, the results of these analyses have not always produced consistent results. Among these factors, three have been shown most consistently to predict a positive response: fewer hospitalizations preceding treatment; an episodic course characterized by an illness pattern of mania, followed by depression, and then euthymia; and a later age at onset of BP. In Figure 1 we show a re-analysis of the Kleindienst meta-analysis of the strongest clinical predictors, including several more recent papers on age at onset not included in their study.

The clinical course of illness prior to initiation of lithium has been shown to be an important predictor of response. For instance, an episodic course of BP has generally been positively correlated with response. Garnham and colleagues performed a retrospective chart review of 120 patients with BP who were treated in an outpatient setting [Garnham *et al.* 2007]. Among the 78 lithium treatment trials considered, a full response to lithium was observed 30% of the time, whereas the rate of partial improvement was 58%. Of the patients who achieved a full

Table 2. Selected studies of clinical predictors of lithium response.

Authors	Year	N	Phase and duration of treatment	Li level	Design	Clinical variable(s)	Outcome evaluation	Findings
Dunner and Fieve	1974	55	Prophylaxis ≥6 months	0.7–1.2 mEq/liter	Case–control	Age of illness onset	Recurrence of mood episodes; poor response defined as patient hospitalized, required tx, or sx present for ≥2 weeks	Age of illness onset not related to Li response (<i>p</i> value NA)
McKnew <i>et al.</i>	1981	6	Acute tx, 16–18 weeks in duration	0.8–1.2 mEq/liter	Double-blind, crossover	Family history of Li responsiveness	Improvement in CPRS, CARS, Conner's TRS, and global rating of child's status	2 children with BP, mixed, who had Li responsive relatives were deemed responsive to Li ($p < 0.05$ for first child's change in global rating; <i>p</i> -value NA for second child.)
Sarantidis and Waters	1981	46	Prophylaxis ≥2 years	NA	Case–control	Age of illness onset	Reduction in time spent in hospital under Li tx; excellent response defined as no hospitalizations during Li tx	Age of illness onset not related to Li response (<i>p</i> value NA)
Yang	1985	101	Prophylaxis >2 years	Mean level 0.73 mEq/liter	Case–control	Age of illness onset	Reduction of episode frequency and/or admissions; patients with good response had no episodes under Li tx	Age of illness onset not related to Li response (<i>p</i> value NA)
Maj <i>et al.</i>	1986	69	Prophylaxis, 2 years in duration	0.30–0.50 mEq/liter (sub-group analysis)	Cohort study	Age of illness onset	Recurrence of mood episodes on Li; patients who responded to Li had no relapses of mood disorder under Li tx	Age of illness onset not related to Li response (<i>p</i> value NA)
Okuma	1993	215	Prophylaxis ≥2 years	NA	Case–control	Age of illness onset	Time ill under Li tx; markedly effective response was defined as complete suppression of mood episodes	Age of illness onset not related to Li response (<i>p</i> value NA)

Grof <i>et al.</i>	1994	1024	Prophylaxis, 3–20 years in duration	≥ 0.7 mEq/liter	Cohort study	Family history of BP	Recurrence under Li; patients who responded to Li had no further mood episodes during Li tx	BP more common in first-degree relatives of patients who responded to Li compared with those who did not respond, ($p = 0.005$)
Kusalic and Engelsmann	1998	29	Prophylaxis, 2 years in duration	0.8–1.3 mEq/liter	Prospective	Quality of BP symptomatology	Recurrence of mood episodes and presence of interepisodic sx during Li tx	Classic sx of mania present in 85% of patients who responded to Li compared with those with those who did not respond ($p < 0.028$)
Yazici <i>et al.</i>	1999	141	Prophylaxis ≥ 3 years	NA	Case–control	Age of illness onset	AMI during Li tx: good response group had AMI < 0.2	Greater age of disease onset associated with better Li response ($p = 0.02$)
Coryell <i>et al.</i>	2000	186	Prophylaxis ≥ 26 weeks	NA	Cohort study	Age of illness onset	Change in morbidity: low morbidity on Li considered marker for Li response	Greater age of disease onset associated with better Li response ($p = 0.0023$)
Kato <i>et al.</i>	2000	32	Prophylaxis > 1 year	0.3–1.0 mEq/liter	Case–control	Age of illness onset	Recurrence under Li; patients who responded had no mood episodes under Li tx	Age of illness onset not related to Li response (p value NA)
Schurroff <i>et al.</i>	2000	97	Prophylaxis ≥ 1 year	NA	Not described	Age of illness onset	Recurrence under Li; response defined as relapse once Li stopped after ≥ 1 year of tx or no relapse of illness after 3 years of tx	Later disease onset (> 40 years) associated with better Li response compared with younger disease onset (< 18 years) ($p = 0.04$)
Tondo <i>et al.</i>	2001	360	Prophylaxis ≥ 1 year	Mean level 0.615 mEq/liter	Cohort study	Age of illness onset	Response defined as less time ill during Li tx	Greater age of disease onset associated with better Li response ($p = 0.005$)
(continued)								

Table 2. Continued.

Authors	Year	N	Phase and duration of treatment	Li level	Design	Clinical variable(s)	Outcome evaluation	Findings
Grof <i>et al.</i>	2002	170	Prophylaxis ≥ 1 year	NA	Case-control	Family history of Li responsiveness	Alda tx response scale; score ≥ 7 indicates full tx response	67% of BP relatives of patients who responded to Li responded themselves compared with 35% in the control group ($p = 0.014$) Patients who responded to Li had 13 first-degree relatives with BP compared with 4 and 6 relatives with BP of patients who responded to lamotrigine and olanzapine respectively (p value NA, but difference statistically significant)
Grof	2003	868	Prophylaxis ≥ 3 years	NA	Cross-sectional assessment of first-degree relatives	Family history of BP	Alda tx response scale; score ≥ 7 indicates full tx response	Episodic course observed in 86% of patients who showed full response compared with 14% who showed full response with minor, residual pretx sx ($p < 0.001$); among patients who responded to Li, 16.6% of first-degree relatives had BP compared with 2.5% of such relatives of patients who responded to lamotrigine ($p = 0.05$) Li was less effective for rapid cycling BP, but so were the anticonvulsants. No clear difference
Passmore <i>et al.</i>	2003	164	Prophylaxis, duration NA	NA	Family study	Pretx episodic illness course Family history of BP	Alda tx response scale; response defined as full stability during tx period with no episodes of abnormal mood	
Tondo <i>et al.</i>	2003	1856	Prophylaxis ≥ 4 months	NA	Review paper with meta-analysis	History of rapid-cycling BP	Rates of tx failure based on recurrence and nonimprovement under tx	

Kleindienst <i>et al.</i>	2005	1138 677 400 1151 904	Prophylaxis ≥1 year	NA	Review paper with meta- analysis	Age of illness onset; no. of previous hospitalizations; CC illness course; DMI illness course; MDI illness course	Variable, as per original publications	for any specific medication emerged. High age of onset correlated with Li response: ($r = 0.11$, $p = 0.003$); high number of previous hospitalizations correlated with poor Li response ($r = -0.35$, $p < 0.001$); CC course negatively correlated with Li response ($r = -0.21$, $p < 0.001$); DMI course negatively correlated with Li response ($r = -0.12$, $p = 0.02$); MDI course positively correlated with Li response ($r = 0.20$, $p < 0.001$)
Duffy <i>et al.</i>	2007	15	Prophylaxis ≥1 year	≥0.7 mEq/liter	Case-control	Family history of Li responsiveness	Alda tx response scale; score ≥7 indicates full tx response	All patients who responded to Li ($n = 9$) had Li-responsive parents ($n = 10$) ($p = 0.001$)
Garnham <i>et al.</i>	2007	120	Prophylaxis ≥6 months	NA	Chart review	Age of illness onset Pretx episodic illness course	Alda tx response scale; score ≥7 indicates full tx response	Younger age of disease onset associated with better Li response ($p = 0.03$); episodic course observed in 44% of patients who had full response to Li compared with 15% in those with nonepisodic course ($p = 0.004$)
Rybakowski <i>et al.</i>	2007	111	Prophylaxis ≥5 years	NA	Case-control	Age of illness onset	Reduction in episode index; excellent response in patients with no mood episodes under tx	Age of illness onset not related to Li response (p value NA)
(continued)								

Table 2. Continued.

Authors	Year	N	Phase and duration of treatment	Li level	Design	Clinical variable(s)	Outcome evaluation	Findings
Berghofer <i>et al.</i>	2008	242	Prophylaxis, average duration of tx 10 ± 6.4 years	≥0.5 mEq/liter	Cohort study	Quality of BP symptomatology	Total MI, depressive MI, and manic MI	Of the 242 patients studied, 142 had more typical sx's of BP than atypical sx's. There was no significant difference between the total MI ($p=0.17$), depressive MI ($p=0.198$), and manic MI ($p=0.47$) based on the quality of BP symptomatology. Greater age of disease onset associated with better Li response ($p<0.01$)
Masui <i>et al.</i>	2008	161	Prophylaxis ≥1 year	0.4–1.2 mEq/liter	Case–control	Age of illness onset	Recurrence under Li; patients who responded had no mood episodes under Li tx	
Backlund <i>et al.</i>	2009	100	Prophylaxis, average duration of tx 9.7 ± 5.8 years	0.5–0.9 mEq/liter	Retrospective, life chart method	Quality of BP symptomatology	Four measures: no. mood episodes/year before/after start of Li; difference in annual burden of illness before/after start; total remission for >3 years after start; burden of illness after start	Absence of mixed episodes prior to Li (RR 3.5) and absence of rapid cycling prior to Li (RR 7.3) predicted good response defined as absence of mood episodes during first 3 years of Li initiation; absence of mixed episodes prior to Li (RR 2.8) and absence of rapid cycling prior to Li (RR 9.6) predicted good Li response defined as low disease burden after start of Li tx

AMI, Affective Morbidity Index; BP, bipolar disorder; CARS, Children's Affective Rating Scale; CC, continuous cycling; CPRS, Children's Psychiatric Rating Scale; DMI, depression–mania-free interval; Li, lithium; MI, morbidity index; MDI, mania–depression-free interval; NA, not available or not applicable; no., number; pretx, pretreatment; RR, relative risk; sx, symptoms; TRS, Teacher's Rating Scale; tx, treatment.

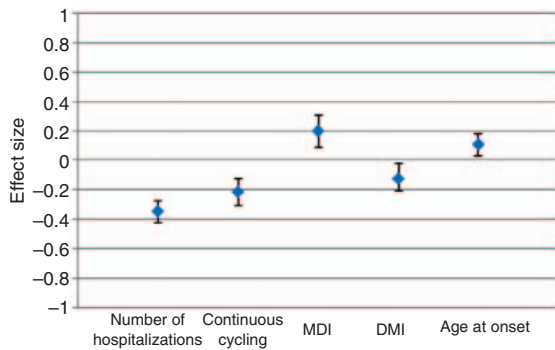


Figure 1. Correlation between clinical predictors and response to lithium treatment. Shown is the meta-analytic effect size (r) for the clinical predictors by descending order of strength. A positive r value indicates a positive correlation between the clinical predictor and a positive response to lithium. A negative r value indicates a negative correlation between the clinical predictor and a positive response to lithium. Meta-analysis performed under a random effects model as described by Kleindienst and colleagues [Kleindienst *et al.* 2005]. The result for age at onset has been updated to include three additional papers examining this relationship. DMI, depression-mania-free interval; MDI, mania-depression-free interval.

response to lithium, 44% were found to have an episodic course of illness prior to initiating treatment compared with 15% in those with a non-episodic course. In a retrospective study of 14 patients who had full stability in their mood while taking lithium, it was noted that nearly 90% of these patients had an illness course characterized by full remission between mood episodes [Passmore *et al.* 2003].

Furthermore, the pattern of mood episodes has also been shown to predict lithium response. Specifically, a pattern of mania (M), depression (D), and euthymic interval (I) has been shown to positively predict lithium response. In their review paper, Kleindienst and colleagues offered an impressive analysis of 42 potential clinical predictors of lithium response, and included in their analysis was a comparison of the MDI and DMI patterns of BP [Kleindienst *et al.* 2005]. The authors concluded based on aggregated data that the MDI pattern is a positive predictor of response, while the DMI pattern was negatively correlated to lithium response.

A family history of BP has been shown to be another favorable predictor of response to lithium, based on studies extending back to the

1970s [Grof *et al.* 1994]. In his review paper, Grof and colleagues cite a study in which family history was obtained on 756 first-degree relatives of 112 patients who demonstrated an unequivocal response to lithium, lamotrigine, or olanzapine [Grof *et al.* 1994]. In the patients who responded to lithium, there was a higher rate of BP in their relatives compared with the relatives of patients who responded to lamotrigine and olanzapine. Passmore and colleagues found a higher prevalence of BP in 103 first-degree relatives of 14 cases with an unequivocal lithium response compared with those who responded to lamotrigine [Passmore *et al.* 2003]. Another study examined 903 first-degree relatives and spouses of 121 patients with BP, major depression, or schizoaffective disorder [Grof *et al.* 1994]. The results of the study likewise demonstrate a greater frequency of BP in the family members of patients who responded to lithium.

There is also some evidence that patients with a family history of response to lithium are more likely to respond as well. The first study to report on familial correlation of lithium response involved just six children of parents who responded to lithium. The two children in the study who had BP both had clear responses to lithium [McKnew *et al.* 1981]. In the only sizable study of familiarity of lithium response, 24 BP relatives of patients who responded to lithium were assessed, along with 40 lithium-treated patients from an outpatient clinic. The prevalence of unequivocal response among the relatives was 67%, as compared with a response rate of 35% in the comparison clinic group [Grof *et al.* 2002]. More recently, Duffy, and colleagues examined 15 adolescents who met criteria for bipolar spectrum disorder and had a parent with BP. Nine of the adolescents were observed to have a positive response to lithium treatment; this observation was associated with lithium responsiveness in the parents [Duffy *et al.* 2007].

Historically, the presence of classic symptomatology of BP, such as euphoric mania, has been considered to prognosticate a good response to prophylactic lithium. In a prospective trial of 29 patients over the course of 2 years, classic manias consisting of euphoria and flight of ideas were associated with lithium response [Kusalic and Engelsmann, 1998]. Furthermore, patients with atypical features of BP, such as rapid cycling and mixed states, have been thought to poorly

respond to lithium treatment. In support of this viewpoint are the findings of a retrospective analysis of 100 patients with BP that employed the semi-structured life-charting protocol [Backlund *et al.* 2009]. The authors demonstrated that the absence of rapid cycling and mixed episodes prior to the initiation of treatment predict a good response to lithium.

However, some more recent work has questioned whether atypical features of BP truly predict poorer outcomes with lithium or poorer outcomes than for other medications. One study followed 242 patients prospectively for a mean period of 10 years [Berghofer *et al.* 2008]. The authors surveyed the patients for atypical features of BP such as mood-incongruent psychosis and the presence of residual, subsyndromal symptoms between mood episodes. Among the study participants, 142 demonstrated more typical features of BP than atypical, while 100 displayed more atypical features than typical or had an equal number of typical and atypical features. Despite these differences in clinical presentation, both groups had similar responses to prophylactic lithium treatment as measured by the mean morbidity index. Another study performed a meta-analysis of 16 studies and 1856 patients demonstrated that those with rapid-cycling BP were less responsive to lithium, but also to anticonvulsant mood stabilizers, compared with patients with nonrapid-cycling illness [Tondo *et al.* 2003]. Importantly, this analysis found no clear evidence to suggest that the anticonvulsants confer better treatment outcomes than lithium in patients with rapid-cycling BP.

The relative frequency of different mood episodes prior to the initiation of treatment with a mood stabilizer has also been investigated. It has been argued that a predominance of depressive episodes over manic episodes prior to the initiation of lithium is associated with better lithium responsiveness. Evidence for this viewpoint includes the findings from a retrospective study of 141 patients with BP: a greater ratio of pre-treatment manic to depressive episodes predicted a worse response to lithium [Yazici *et al.* 1999]. However, Kleindienst and colleagues aggregated data from two studies consisting of 147 patients and concluded that neither the number of previous manic episodes nor depressive episodes was associated with lithium response [Kleindienst *et al.* 2005].

Predictors of lithium response: biologic studies

Numerous biologic variables, ranging from cerebrospinal fluid levels of central nervous system metabolites to changes in the potential difference across rectal mucosa, have been studied as potential biologic predictors of lithium response. While the hope has been that a simple laboratory test might predict lithium response, decades of research on this topic have yet to identify a biologic measure of unequivocal clinical utility. However, the identification of biologic predictors of lithium response remains an important step in the pursuit of personalized medicine for the treatment of BP. The goal of this section is to review promising biologic markers of response based on key neurophysiologic and neuroimaging findings.

In the realm of neurophysiology, electroencephalography (EEG) is attractive because it is a non-invasive test of brain function. It seems reasonable to hypothesize that lithium response might be associated with EEG findings given that several other mood stabilizers are antiepileptic agents. However, only a few studies have examined the relationship between EEG and lithium response. In one such study, the EEG recordings of 27 patients taking lithium for BP were examined [Ikeda *et al.* 2002]. None of the five patients who responded to lithium were found to have abnormal EEGs, while five of the 22 patients who did not respond to lithium showed an abnormality. Reeves and colleagues examined relative EEG differences in 20 patients who responded to lithium and 20 patients who responded to valproate who presented for treatment during a manic episode [Reeves *et al.* 2001]. Seventy percent of the patients who responded to valproate were found to have EEG abnormalities, while only 30% of those who responded to lithium had abnormal EEGs. Thus, the authors concluded that patients with EEG abnormalities were more likely to respond to valproate than lithium. In another series of papers, patients who did not respond to treatment were found to have increased generalized theta activity at baseline [Small *et al.* 1999, 1998]. However, the group who did not respond to treatment consisted of patients who received five different psychotropic regimens, such as lithium monotherapy or combination therapy with lithium and haloperidol. Thus, this EEG finding was not specific to lithium treatment.

Event-related potentials (ERPs) have also been examined as a possible predictor of lithium response. ERPs, which are measured by EEG, assess changes in brain activity following the application of sensory stimuli. Among the initial evidence for this predictor was a pilot study that demonstrated greater intensity dependence of the N1/P2 component of auditory evoked potentials in patients who responded to prophylactic lithium therapy [Hegerl *et al.* 1987]. This group subsequently confirmed these results in a replication study of 34 patients with affective illness [Hegerl *et al.* 1992]. In another study, stronger loudness dependency of auditory-evoked potentials (LDAEPs) of the primary auditory cortex was associated with a positive response to prophylactic lithium in a study of 30 patients with major depression and BP [Juckel *et al.* 2004]. Further, the authors studied lithium response among patients with BP and similarly found greater LDAEPs of the primary auditory cortex in patients who responded compared with those who did not respond. These studies suggest that ERPs may serve as a clinically useful predictor of lithium response, although several caveats make it hard to draw firm conclusions: the studies were small; they measured different aspects of ERPs; and they included patients with both unipolar depression and bipolar disorder.

Neuroimaging is another promising tool for *in vivo* investigation of lithium response in BP. In addition to its noninvasive methodology, brain imaging confers other advantages. For example, certain imaging techniques, such as magnetic resonance spectroscopy (MRS), can be repeated serially because the scans do not subject the patient to ionizing radiation. Further, neuroimaging permits the study of brain mechanisms underlying mood disorders, as well as the therapeutic action of lithium. Thus, it is anticipated that brain imaging will facilitate the identification and investigation of rational biologic predictors of lithium response. Table 3 summarizes some of the most promising results to date in this area.

The therapeutic action of lithium is unknown, but one hypothesis is that lithium treatment may dampen overactive neural networks in BP by depleting myo-inositol (mI), a component of the phosphoinositide second messenger system. Thus, mI has been considered a target in studies examining lithium response. Moore and colleagues examined the relationship between mI,

as measured by quantitative MRS, and lithium treatment response in 12 patients with depression and BP [Moore *et al.* 1999]. The mI levels in the right frontal lobe decreased by approximately 30% after 5–7 days of lithium treatment and remained reduced after 3–4 weeks of treatment. However, the authors concluded that reduction in mI levels did not predict therapeutic response to lithium because mI levels dropped prior to a significant improvement in the patient's clinical state. A subsequent study investigated mI levels in 11 children with BP who were treated with lithium in comparison to baseline scans from 11 gender and age-matched controls using proton MRS [Davanzo *et al.* 2001]. After 1 week of treatment, patients who responded to lithium were noted to have reduced anterior cingulate mI levels compared with pretreatment levels.

Neuroimaging has also permitted structural correlations of lithium administration (Table 3). Lithium treatment has been associated with increased gray matter volumes in general [Moore *et al.* 2000], and in particular brain regions such as the hippocampus [Foland *et al.* 2008; Yucel *et al.* 2007], and the amygdala [Usher *et al.* 2010; Foland *et al.* 2008]. Recently, several studies have examined whether such gray matter changes correlate with lithium response rather than simply treatment. One study revealed that a favorable clinical response in BP was associated with persistently increased cerebral gray matter volume over the course of 16 weeks of treatment [Lyoo *et al.* 2010]. A second studied 28 patients with BP longitudinally for 4 weeks and determined that patients who responded to lithium had increased prefrontal gray matter compared with those who did not respond [Moore *et al.* 2009].

Predictors of lithium response: molecular genetics studies

Molecular genetics as the basis for predicting response to medication has become an area of intensive investigation, particularly because it holds enormous promise as the basis for personalized medicine. This concept has its origin in the work of Archibald Garrod, the English physician-scientist who coined the term 'chemical individuality'. Barton Childs, of Johns Hopkins, was much influenced by Garrod. Childs, who made a major impact in human genetics, with his work on the X chromosome and its diseases, wrote a book called *Genetic Medicine: A Logic of Disease*

Table 3. Neuroimaging studies of the relationship between structural changes and lithium treatment and response.

Authors	Year	N	Design	Li treatment	Li level	Independent variable	Outcome variable	Findings
Moore <i>et al.</i>	2000	10	Prospective	4 weeks	~0.8 mEq/liter	Li tx	Gray matter volume	~3% mean increase in total gray matter volume in 8/10 patients with BP treated with Li for 4 weeks (p value NA)
Yucel <i>et al.</i>	2007	12	Prospective	Prophylactic, 2–4 years' duration	Mean Li level at baseline 0.5 mEq/liter	Li tx	Hippocampal volume	Equal increases in mean right and left hippocampal volumes noted. Total hippocampal volume increase over time significant ($p < 0.001$). Larger total amygdala and hippocampal volumes noted in Li-treated patients compared with patients without Li ($p = 0.023$ and $p = 0.008$ respectively)
Foland <i>et al.</i>	2008	49	Cross-sectional	NA	NA	Li tx	Hippocampal and amygdala volume	Increased prefrontal cortex gray matter volume after 4 weeks of Li in patients who responded to tx ($p = 0.003$)
Moore <i>et al.</i>	2009	28	Prospective	4 weeks	~0.8 mEq/liter	Li response defined as >50% reduction in HAM-D total score	Gray matter volumes of total brain, prefrontal cortex, and left subgenual cortex	Greater right amygdala volumes observed in patients with BP treated with Li compared with patients with BP without Li tx and healthy controls ($p < 0.02$)
Usher <i>et al.</i>	2010	82	Cross-sectional	NA	Mean level 0.72 mEq/liter in Li group	Li tx	Amygdala volume	Reduction in depressive symptoms corresponded to rate of gray matter volume increase in patients treated with Li ($p = 0.03$)
Lyo <i>et al.</i>	2010	36	Prospective	Mean Li tx 81.8 days	Mean level 0.65 mEq/liter in Li group	Li response, defined as reduction in depressive symptoms	Cerebral gray matter volume	
HAM-D, Hamilton Depression Rating Scale; Li, lithium; NA, not available or not applicable; tx, treatment.								

(Childs, 1999), which lays out the basis for personalized medicine. Childs commented:

With the idea of common management [of disease], we've tended to see patients as similar, and we've tended to treat not the patient but the disease. I'm hoping that recognition of individuality in each person may cause physicians to pay more attention not to the disease but to the patient who has the disease, and maybe even change the treatment a little bit to take into account the uniqueness of the individual.

Throughout medicine, however, there are, to date, surprisingly few useful genetic tests for treatment of common diseases. Nonetheless, there are a few of them, most prominently in cancer. Two major examples are the use of genetic testing to guide clinical decisions about the use of trastuzumab (Herceptin) [Genentech, San Francisco, CA] in breast cancer, and *KRAS* in colorectal cancer [Lievre *et al.* 2006; Pietras *et al.* 1994]. No useful genetic tests exist yet that can guide the treatment of major psychiatric illnesses, and BP is no exception. However, molecular genetic studies of lithium response to date have been small and relatively few in number.

A number of small genetic association studies have analyzed the relationship of variation in biological candidate genes to lithium response. These are studies that typically have examined one or several genes that could plausibly be involved in lithium response because of some known or suspected role in the pathophysiology of BP or in the mechanism of action of the drug. A number of studies have examined lithium response in BP in this way. The studies have mostly utilized sample sizes that were only in the dozens, although a few were in the hundreds. Many investigators believe that samples in the thousands may be necessary to see the kind of subtle genetic effects likely to be involved in predicting drug response.

These studies have all reported either negative findings or positive findings that are modest and unconfirmed. Negative findings have been reported for the dopamine type 2, 3, and 4 receptors; for the serotonin type 1A, 2A, and 2C receptors; and for the GABAA- α -1, *INPP1*, and PLC- γ 1 genes [Serretti, 2002]. A study of the tryptophan hydroxylase gene found a worse lithium response for patients with the A/A variant of a gene marker, though

this difference was only marginally significant [Serretti *et al.* 1999]. One published study of the serotonin transporter gene found a significantly worse response in patients carrying two copies of the short allele in the promoter region polymorphism [Serretti *et al.* 2001]. Several studies have examined the brain-derived neurotrophic factor (*BDNF*) gene. Two studies reported that excellent response was found in patients who carried particular variants in *BDNF* [Dmitrzak-Weglarz *et al.* 2008; Rybakowski *et al.* 2005]. However, Masui and colleagues had negative findings in a Japanese sample [Masui *et al.* 2006b], and Michelon and colleagues' results were also negative [Michelon *et al.* 2006]. Another study found modest evidence implicating the *BDNF* receptor gene *NTRK2* in lithium response, though the association was seen only for patients with a subtype of illness [Bremer *et al.* 2007].

XPB1, which encodes the X-box binding protein 1, is an important molecule in the endoplasmic reticulum stress response. There is a variant in the promoter region of the gene, called -116C/G, shown to influence *XPB1*-dependent transcription activity in lymphoblastoid cells [Kakiuchi *et al.* 2003]. In another study the same authors suggested that lithium may not be effective for patients with BP who carry the G/G genotype of *XPB1* [Kakiuchi and Kato, 2005]. A second Japanese group showed that patients with the C allele were significantly more likely to be classed as responsive to lithium compared with those lacking a C allele [Masui *et al.* 2006a]. Interestingly, Kim and colleagues found that the opposite allele, of *XPB1*-116C/G, was associated with a better prophylactic treatment response to valproate in patients with BP. While intriguing, the numbers in these studies are quite small, and thus these results await replication in larger samples [Kim *et al.* 2009].

Recently, the first genome-wide association study was done to identify single nucleotide polymorphisms (SNPs) that would predict lithium response, from among hundreds of thousands of genetic variations covering most of the genes in the genome [Perlis *et al.* 2009]. A total of 458 patients treated with lithium from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) cohort were studied, with follow up in 359 patients with BP treated with lithium in a second cohort from the University College London. Time to recurrence of a mood

episode was the outcome or phenotype variable for the first cohort, while a dichotomous poor *versus* intermediate or good response was the outcome in the second. No definitive results were identified in this study, perhaps because the study was underpowered (Figure 2). However, several regions of potential interest were found. One of these spanned a gene coding for the AMPA type glutamate receptor *GRIA2*, for which expression has been shown to be regulated by lithium treatment. Additional genes of potential interest were: *SDC2* or Syndecan-2, which codes for a cell-surface proteoglycan shown to play a central role in the formation of dendritic spines in the hippocampus; *SV2B*, synaptic vesicle glycoprotein-2B, a protein expressed primarily in the hippocampus; and *ODZ4*, the human homologue of *Drosophila* odd Oz (*odz*)-4, implicated in brain patterning.

Future directions

One major new effort to study lithium genetics stems from the Consortium for Lithium Genetics (www.ConLiGen.org), formed in 2008 by researchers from the International Group for the Study of Lithium-Treated Patients (www.IGSLI.org) and the Unit on the Genetic Basis of Mood and Anxiety Disorders at the US National Institute of Mental Health (NIMH). Led by Thomas Schulze and Francis McMahon, this consortium has assembled the largest sample to date for genome-wide studies of lithium response in BP, currently comprising more than 1200 patients characterized for

response to lithium treatment [Schulze *et al.* 2010]. This collaboration is basing its phenotype definition on the scale developed by Martin Alda, a leading lithium response researcher at Dalhousie University in Canada, which rates lithium response from 0 to 10, subtracting points for confounding factors such as poor compliance or need for additional medications while on lithium. Use of this scale is important because definitions of lithium response have varied widely in the literature. An initial goal of ConLiGen is to perform a genome-wide association study on this large assembled dataset.

A second major new initiative in lithium genetics is just getting under way in the USA under the leadership of John Kelsoe, a psychiatrist and leading BP geneticist at the University of California, San Diego. This project is an outgrowth of the NIMH Genetics Initiative Consortium for Bipolar Disorder, a collaboration involving up to 11 US sites. The new study, being conducted in the context of the Pharmacogenetics Trials Network of the NIH, will include many of those sites, and also international collaborators and clinical trials experts. This project, which will be carried out in coordination with ConLiGen, also aims to conduct genome-wide association studies of lithium response in BP. This study will, in addition, have a smaller divalproex sodium arm, so that it might shed light on genes that differentially predispose to response to these two major BP medications.

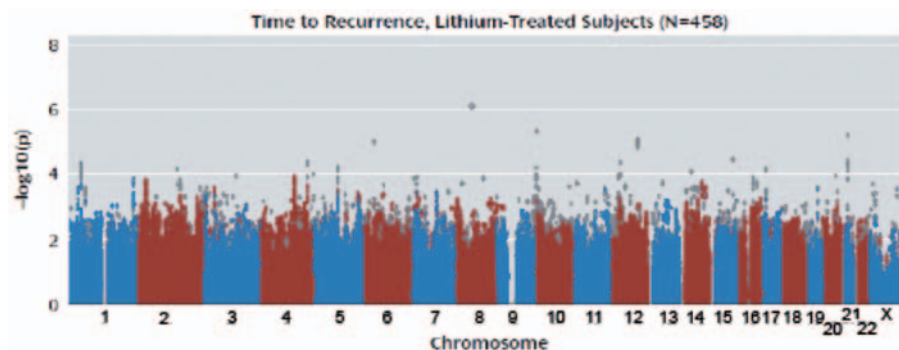


Figure 2. Genome-wide association study of lithium response. This figure, called a Manhattan plot, shows the results of testing hundreds of thousands of genetic variations across the genome in patients taking lithium. The x axis shows the location of each on one of the 23 chromosomes. A test was performed to determine whether each variant was associated with the time to recurrence of a mood episode while on medication. The y axis shows the strength of association, with the $-\log_{10} p$ value of 8–9 being the range where findings are considered definitive. Each dot represents one genetic variant, and most of them are clustered in the y-axis range of 0–3, so that they are depicted as coalesced into solid bars. The strongest finding reaches just over 6, on chromosome 7. [Reproduced with permission from Perlis *et al.* 2009].

Finally, new studies are getting under way that would perform brain imaging of the same patients who are being characterized for lithium response, and also being genotyped for genome-wide association studies. This additional characterization might provide important information that could help clarify the mechanisms through which genetic variation leads to variation in clinical response.

Conclusions

In summary, fewer hospitalizations preceding treatment, an episodic course characterized by an illness pattern of mania followed by depression, and a later age of disease onset are important clinical predictors of a favorable response to lithium. While several biologic predictors have been studied, the results are preliminary and require replication with studies consisting of larger patient samples over longer observation periods. Neuroimaging is a particularly promising method given that it might concurrently illuminate pathophysiologic underpinnings of BP, the mechanism of action of lithium, and potential predictors of lithium response. One genome-wide association to date using lithium response as a phenotype did not yield any definitive results, though the small sample size did not provide substantial power.

With major new initiatives in progress aiming to identify genes and genetic variations associated with lithium response, there is much reason to be hopeful that clinically useful information might be generated within the next several years. This could ultimately translate into tests that could guide the choice of mood stabilizing medication for patients. In addition, it might facilitate the development of newer, more effective medications that could act more quickly and yield fewer side effects. The addition of brain imaging signatures of lithium response could provide additional valuable information that might help in several ways: by more powerfully predicting response in conjunction with genetic variations, by serving as a biomarker of response in clinical trials, and by illuminating pathophysiological pathways from gene to clinical response.

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Conflict of interest statement

The authors have no conflicts of interest in preparing this article.

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