Factors predicting inefficacy of lithium in patients with Bipolar I Disorder

Master Thesis - Clinical and Health Psychology

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ABSTRACT

Introduction: The aim of this study was to investigate whether factors, that are related to a more severe course of bipolar disorder, will predict the efficacy of lithium in BPI patients. For this purpose it was examined whether earlier onset, comorbid anxiety, comorbid alcohol dependence, comorbid substance dependence and early extreme adversity predict lithium response in a large sample of BPI patients.

Method: Based on a questionnaire about lithium response, 446 lithium users were selected and groups were created: A group that used lithium at the time of inclusion and was (very) satisfied with the performance, versus a group that once used lithium but discontinued the treatment because of inefficacy. Furthermore an additional group was created which contained all patients who discontinued lithium treatment due to reasons other than inefficacy, including motivation and negative side effects.

Results: As expected, the current study found an association between lifetime alcohol dependence and bad lithium response, alcohol dependence was associated with the discontinuation of lithium treatment due to motivational reasons and due to inefficiency. However, none of the other factors of the severity profile i.e. earlier onset, comorbid anxiety, comorbid substance dependence and early extreme adversity were related to bad lithium response.

Discussion: Apart from alcohol dependence, the severity profile appeared unusable for drafting a predictive model for discontinuation of lithium treatment. This makes further research based on other profiles necessary. However, the results may reflect an influence of motivation on lithium treatment in BPI patients with comorbid alcohol dependence. Therefore, strictly monitoring motivation for treatment and enhancing compliance within this group should be an essential component in treatment with lithium.

Keywords: Bipolar I disorder, lithium, severe course, motivation, earlier onset, anxiety, alcohol dependence, substance dependence, early adversity

Bipolar disorder is a severe, lifelong affective disorder. It is characterized by recurrent episodes of mania, hypomania, depression, or mixed episodes (Merikangas et al., 2007). Among the psychiatric disorders it is associated with some of the highest levels of disability, comorbidity and suicidality (Judd et al., 2008). The estimated lifetime prevalence of bipolar disorder ranges from 1,5 to 2% (Pini et al., 2005). Classification of bipolar disorder is in most cases based on criteria published in the Diagnostic and Statistical Manual of Mental Disorders, DSM. In the text revision of the fourth edition (DSM-IV-TR; APA, 2000), bipolar disorder type 1 (BDI) diagnosis requires the presence of at least one manic or mixed episode. bipolar disorder type 2 is diagnosed when, besides one or more depressive episodes, at least one hypomanic episode, but never a mania has occurred.

Bipolar disorder can be managed with a variety of pharmacological and psychotherapeutic treatments, in which the maingoals are the acute management of depressive and manic episodes and prevention of future episodes (American Psychiatric Association, 2002). Agents that generally decrease the intensity or duration of manic and depressive episodes, and prevent them from occurring, are called mood stabilizers (Grilly & Salamone, 2012). There are four mood stabilizers for which significant evidence of efficacy exists: lithium, valproate, carbamazepine, and lamotrigine (Crossley & Bauer, 2007). Of these, lithium is generally recommended as first-line treatment in current guidelines (Licht, 2012; American Psychiatric Association, 2002), for both treating mania and maintenance therapy (Goodwin, 2009).

Lithium is a light metal ion that exists in nature as a salt. After intake, lithium spreads throughout the entire body thereby passing the blood brain barrier (Grilly & Salamone, 2012). The effectiveness of lithium as a treatment for symptoms of bipolar disorder was discovered by psychiatrist John Cade in the mid-19th century (1949). How lithium induces its mood-stabilizing influence is still uncertain. However there are a number of ideas about the specific mechanism of lithium. Jope (1999) argues that because of its anti-manic, antidepressant and mood-stabilizing effects, it may be expected that there are multiple actions of lithium, rather than a single mode of action. A growing body of evidence supports the idea that lithium exerts its mood-stabilizing effects, at least partially, by activating neurotropic and neuroprotective mechanism (Quiroz, Machado-Vieira, Zarate, & Manji, 2010; Jope, 2003; Rybakowsky, 2011).
Besides the therapeutic effect, there are a number of side effects and drawbacks that come with the use of lithium. The therapeutic index of lithium is narrow; serum levels below 0.4 mmol/L have no therapeutic effect and levels above 1.0 mmol/L are associated with signs and symptoms of lithium toxicity such as confusion, seizures and renal

damage. Lithium toxicity can be life threatening (Collins, Barnes, Shingleton-Smith, Gerrett, & Paton, 2010; Anon, 2005). Even when the level is maintained within the therapeutic range, lithium-use can cause long-term hypothyroidism and damage to the kidney. (Paton et al, 2010). Because of these potential problems treatment guidelines recommend regular checking of serum lithium level throughout the treatment (every 3 – 6 months) to ensure that it remains within the therapeutic range (Collins, Barnes, Shingleton-Smith, Gerrett, & Paton, 2010). This periodic monitoring of blood levels may be inconvenient for patients. Moreover, the risk of weight gain and the risk of side effects like cognitive impairment and/or reduced intensity of perceptions and emotions may be aggravating for patients (Licht, 2012).

Despite the side effects, lithium is - after more than 60 years of use in modern psychiatry - still considered the major agent in both acute treatment, and maintenance treatment of bipolar disorder (e.g. Rybakowsky, 2011; Licht, 2012; Hirschowitz, Kolevzon, & Garakani, 2010; Geddes, Burgess, Hawton, Jamison, & Goodwin, 2004). In large studies on the effectiveness of lithium as maintenance treatment in patients with bipolar disorder, good outcomes are seen in approximately one-third of the subjects (American Psychiatric Association, 2002). The results of the BALANCE study (Geddes, et al., 2010) show that lithium is more likely to prevent relapse than valproate. In a naturalistic observation study which evaluated the effectiveness of commonly used pharmacological treatments for bipolar disorder, the highest rates of full response were observed for lithium. Approximately 30% of patients showed full response and 60% of patients showed partial response (Garnham et al., 2007). The protective effect of lithium seems to be most clear for manic episodes, in which lithium reduces the risk of relapse by about 40%. For depressive episodes protective effects of lithium are less robust: the relative risk reduction of relapse is about 22% (Geddes, Burgess, Hawton, Jamison, & Goodwin, 2004). With respect to clinical efficacy it has been calculated that, in the acute management of mania, for every six patients treated with lithium, one will respond (Storosum, Wohlfarth, Schene, Elferink, Zwieten, & Brink, 2007). These statistics imply that, although lithium seems to be more effective than other drugs, there is a group for whom lithium apparently works insufficiently (Treuer & Tohen, 2010).

Because of this insufficient response in some patients, the effectiveness of lithium was questioned during the last decade of the past century (Kleindienst, Greil, Rüger, & Möller 1999). This critical attitude will also have to do with the previously mentioned side effects and risks, which induce an adverse cost–benefit ratio (Paton et al, 2010; Licht, 2012). Grof (2003; 2010) points out that lithium apparently works very well in some patients, but shows much poorer rates of response in others. The group of patients in

which lithium can completely prevent the recurrence of episodes for ten years or more, are described as 'excellent lithium responders' (Grof, 1999). This group consists of approximately one-third of lithium treated patients (Rybakowski, 2011).

There are a number of factors known for predicting a more severe course of the bipolar disorder. Childhood or adolescent onset is associated with more episodes, more comorbidities, rapid cycling, severe mania and depression, and fewer euthymic days. (Leverich et al, 2007). In addition, earlier onset is associated with greater likelihood of suicide attempts and violence (Perlis et al., 2004). The presence of comorbid anxiety disorders is also related to a worse outcome for bipolar patients compared to those without anxiety disorders (El-Mallakh, & Hollifield, 2008). Patients with comorbid disorders appear to have greater symptom burden, poorer treatment response, more depressive complaints, lower quality of life (Keller, 2005; Otto et al., 2006) and more suicidal ideation (Allen, Chessick, & Miklowitz, 2005). Even greater effects have been found for patients suffering from multiple anxiety disorders (Otto et al., 2006). People with bipolar disorder frequently struggle with substance abuse and dependence. Drug abuse is associated with increased duration and / or severity of mania (Baethge et al., 2005). Subjects with lifetime comorbid substance abuse histories, are hospitalized more often (Cassidy, Ahearn, & Carroll, 2001). It has also been found that cannabis use is associated with more time in affective episodes and with rapid cycling (Strakowski, DelBello, Fleck, Adler, Anthenelli, & Keck, 2007). Last, it is known that a history of early extreme adversity (abuse in childhood or adolescence) is associated with a more severe course (Post, Leverich, Xing, & Weiss, 2001; Dienes, Hammen, Henry, Cohen, & Daley, 2006; Garno, Goldberg, Ramirez, & Ritzler, 2005) and difficulties in treatment (Brown, McBride, Bauer, & Williford, 2005).

Since an early onset, the presence of comorbid anxiety disorders, substance abuse and childhood trauma are associated with a more severe course, manifested by more or severe episodes, lithium may be less able to prevent relapses in patients that meet these criteria. In addition to the above suggested group of 'excellent lithium responders' there seems to be a group of ‘bad lithium responders’. Up until this moment, the difference between these two groups has scarcely been investigated. However, in order to predict optimal treatment, it is useful to search for predicting factors indicating to which of the groups a specific patient might pertain (Kleindienst, Engel, & Greil, 2005).

By using a large sample of BPI patients, the current study will examine whether the a severity profile, based on factors that are related to a more severe course (early onset, comorbid anxiety, early extreme adversity and comorbid substance dependence) will

predict bad lithium response. This will be investigated by comparing a group of patients that discontinued the lithium treatment because of low efficacy versus a group that is currently using lithium to their satisfaction. N.B. In this article 'efficacy' not refers to the pharmacological meaning of the concept, the following definition is used: the quality of being successful in producing an intended result. A significant association is expected for all the predictors. A second question is, whether those same factors will predict discontinuation of lithium treatment due to other reasons than inefficacy. Of this purpose the group of patients currently using lithium with satisfaction will be compared with the patients that stopped the use of lithium treatment due to other reasons than inefficacy (e.g. motivation and side-effects). By answering this second questions it is intended to explore whether the examined factors are predictive for discontinuation of lithium use in general rather than due to inefficacy.

Methods

The current study is part of a larger study: Bipolar Genetics. This study has as a main purpose to identify genetic variation involved in susceptibility of bipolar disorder in a relatively homogeneous Dutch population. For this reason a large cohort of Dutch patients with BPI disorder (and their first or second-degree relatives) are being recruited. The study is approved by the Medical Ethical Committee of the UMC Utrecht.

Participants

Various recruitment methods were used: People who had ever used lithium were approached by their pharmacies and patients were contacted through letters to all members of a Dutch association for patients with bipolar disorder. Participants were also recruited through healthcare centers, the project's website and newspapers.

Inclusion criteria for participation in the study were to have at least three Dutch grandparents (for genetic homogeneity), a minimum age of 18 years and a premorbid IQ of at least 80 (as measured with the national adult reading test). Additionally it was necessary to meet the criteria of BPI according to the DSM IV. There were three exclusion criteria: Presence of a somatic illness that might be of influence on diagnosing bipolar disorder, current treatment or detention under the Dutch governmental mental health act and the inability to speak, read or understand the Dutch language.

Final sample: 743 patients participated in the current study, of which 658 patients had ever used lithium in their lives (Based on Questionnaire for lithium response). A number of patients was excluded due to missing values on Age (2), the CTQ (40), the anxiety section of the SCID-I (26), Alcohol dependence (5), Substance dependence (138), Age of illness onset (7) and due missing information about lithium use/response(39). Therefore the final sample consisted of 446 patients with BPI that had ever used lithium in their

lives, of which 183 males and 263 females. Age ranged from 20 to 79 years with a mean age of 49,65 (*SD* = 11.95).

Table 1 shows the demographic and clinical characteristics of the different groups; G.LR (Good Lithium responders), B.LR (Bad lithium responders), D.OR (Discontinuation of lithium treatment due to other reasons than inefficacy) US/N (Unsatisfied / neutral users) and two different subgroups within D.OR.

Table 1

Demographic and clinical characteristics by group

		G.LR N= 252 (56.5%)	B.LR N= 35 (7.8%)	D.OR N= 86 (19.3%)	US/N N= 73 (16.4%)
Age	*M (SD)*	49 (12)	47 (10)	51 (11)	49 (12)
Age of onset	*M (SD)*	32.00 (10.48)	30.49 (9.92)	31.08 (10.88)	31.64 (12.56)
CTQ-score	*M (SD)*	43.51 (8.62)	44.86 (8.66)	44.35 (8.47)	44.68 (9.36)
Gender					
Male	*N (%)*	96 (38.7)	20 (57.1)	39 (45.3)	28 (38.4)
Female	*N (%)*	152 (61.3)	15 (42.9)	47 (54.7)	45 (61.6)
Anxiety disorders	*N (%)*	57 (23.0)	12 (34.3)	20 (23.3)	14 (19.2)
Alcohol dependance	*N (%)*	51 (20.6)	14 (40.0)	29 (33.7)	25 (34.2)
Substance dependence	*N (%)*	19 (7.7)	3 (8.6)	8 (9.3)	7 (9.6)

		Discontinuation of lithium treatment due to side effects N=30 (9%)	Discontinuation of lithium treatment due to motivational reasons N= 16 (3.6%)
Age	*M (SD)*	51 (11)	52 (12)
Age of onset	*M (SD)*	32.90 (10.56)	29.88 (8.88)
CTQ-score	*M (SD)*	44.05 (6.94)	42.00 (7.28)
Gender			
Male	*N (%)*	18 (45.0)	8 (50)
Female	*N (%)*	22 (55.0)	8 (50)
Anxiety disorders	*N (%)*	31 (77.5)	15 (93.8)
Alcohol dependance	*N (%)*	11 (27.5)	7 (43.8)
Substance dependence	*N (%)*	1 (2.5)	2 (12.5)

Procedure

The study took place at the University Medical Center Utrecht UMCU. First of all participants gave their written consent after receiving a full explanation of the procedures. This visit consisted of the collection of blood samples (for genetic analyses), a structured psychiatric interview (SCID-I, 1996) and filling in questionnaires; the QBP-NL, a questionnaire for lithium response and the MINI and / or the Cidi. This was followed by several subtasks of the WAIS, body measurements (height, weight and blood pressure) and questions about the occurrence of psychiatric disorders in the family. This visit lasted about 3,5 hours. Patients received a reward of 30 euro's and reimbursement of travel expenses. In addition, all participants were asked to complete a set of internet questionnaires at home; The Childhood Trauma Questionnaire - Short Form (CTQ-SF, 1994) and other questionnaires for the main study. Completing these questionnaires took about one and a half hour and could be discontinued and resumed any time. Participants without internet or computer received a paper version. After completion of the questionnaires participants received a reward of 15 euros.

Materials

Questionnaire for lithium response: A questionnaire about lithium response was administered, containing questions about start date of lithium use, statements about the efficacy, rating of satisfaction and, if applicable, why the use of lithium was discontinued. Based on this questionnaire lithium users were selected and groups were created for conducting the analyses. First of all two groups were created; 'good lithium responders' and 'bad lithium responders': A group that used lithium at the time of inclusion and was satisfied or very satisfied with the performance, versus a group that once used lithium but discontinued the treatment because of inefficacy, according to the user. Furthermore an additional group was created: 'Discontinuation of lithium treatment due to other reasons than inefficacy'. This group contains all patients who did not continue lithium treatment due to reasons other than inefficacy, including motivation and negative side effects.

Structured Clinical Interview for DSM-IV axis I disorders: The Dutch adaption (Groenestijn, Akkerhuis, Kupka, Schneider, Nolen) of the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I; First, Spitzer, Gibbon & Williams, 1996) was conducted to verify the BP-I diagnosis. This interview was also used to assess the presence of comorbid anxiety disorders (obsessive-compulsive disorder, post-traumatic stress disorder, social phobia, specific phobia, agoraphobia, panic disorder and generalized anxiety disorder). This method has a moderate to high inter-rater reliability, as indicated

by a mean Kappa of 0.71, for the assessment of Axis-1 disoders (Lobbestael, Leurgans & Amtz, 2011).

The Childhood Trauma Questionnaire: The Childhood Trauma Questionnaire – Short form (CTQ-SF) was used for assessment of child abuse and neglect (Bernstein et al., 1994). It is a self-report inventory with 28 items about traumatic experiences in childhood and adolescence. Questions were answered on a 5-point Likert scale, with response options ranging from 'Never True' (1) to 'Very Often True' (5). The CTQ assessed five clinical scales: physical, sexual and emotional abuse, and physical and emotional neglect, which have been empirically derived (Bernstein et al., 1994). In the current study, a Dutch version of the CTQ was used: the JTV (Jeugd Trauma Vragenlijst; Arnts & Wessel, 1996). This study only used the total score rather than the subscales.

The Questionnaire for Bipolar Illness: The QBP- NL (Bipolar Questionnaire) was used to determine the age of onset of the disorder.

Mini-International Neuropsychiatric Interview: Two sections of the Mini-International Neuropsychiatric Interview (MINI; Van Vliet, Leroy & Megen, 2000) were used to establish diagnosis of alcohol and substance dependence. This method has a moderate to high inter-rater reliability, as indicated by a mean Kappa of 0.67 (Sheehan et al., 1997).

The Composite International Diagnostic Interview: At the start of the study, not the MINI but the Composite International Diagnostic Interview (CIDI; World Health Organization, 1993) was used to provide insight into alcohol and substance use of the participants. The inter-rater reliability of this interview has been demonstrated to be excellent, the test-retest reliability good, and the validity also good (Andrews & Peters,1998). The maximal alcohol consumption per week was obtained for each patient with the CIDI. A maximal weekly alcohol consumption above the World Health Organization [WHO] recommendation (2000) of 280 gram for men and 168 gram for women was marked as hazardous alcohol intake. Since an alcoholic consumption contains 10 grams of alcohol on average, a cutoff score of 28 glasses for men and 17 glasses for women was held.

Combining MINI and CIDI: From some of the participants, both MINI and CIDI scores for alcohol and substance use were obtained. A medium correlation was found between the variable based on the CIDI and alcohol dependence according the MINI. For this reason it was decided to combine the two variables into one variable. In case patients scored positive on one of the variables, the combined variable would be positive too. For substance dependence the correlation between the MINI and CIDI appeared to be large. So these two variables were combined into one variable as well.

Statistical Analysis:

For conducting statistical analyses, Statistical Package for the Social Sciences (SPSS Inc, version 20.0) was used two different analyses were conducted.

1. Factors predicting inefficacy of lithium

To examine whether age of illness onset, presence of comorbid anxiety disorders, comorbid alcohol dependence, comorbid substance dependence and history of early extreme adversity, which are related to a more severe course, indeed predict to which of the two groups ('good lithium responders' versus 'bad lithium responders') patients pertain, a logistic regression analysis was conducted. Group was the outcome variable ('good lithium responders' versus 'bad lithium responders'). Age of illness onset, presence of comorbid anxiety disorders, comorbid alcohol dependence, comorbid substance dependence and history of early extreme adversity were used as predictor variables. Age and gender served as covariates in this analysis.

2. Factors predicting discontinuation of lithium treatment due to other reasons than inefficacy

A additional intention was to explore whether age of illness onset, presence of comorbid anxiety disorders, comorbid alcohol dependence, comorbid substance dependence and history of early extreme adversity are predictive for discontinuation of lithium use in general rather than due to inefficacy. Of this purpose a subsequent analysis was performed to examine whether those factors will predict discontinuation of lithium treatment due to other reasons than inefficacy (e.g. motivation and side-effects). Again a logistic regression analysis was conducted. Group was the outcome variable ('good lithium responders' versus 'discontinuation of lithium treatment due to other reasons than inefficacy), Age of illness onset, presence of comorbid anxiety disorders, comorbid alcohol dependence, comorbid substance dependence and history of early extreme adversity were used as predictor variables. The covariates in this analysis were, age and gender.

Before the analyses, preliminary checks were conducted to ensure the assumptions of linearity, independent errors and multicollinearity were not violated. Data was checked for outliers using Cook's distance, no outliers were found.

Results

1: Factors predicting efficacy of lithium

To test whether the factors that are related to a more severe course are predictive for the efficacy of lithium, a logistic regression was performed. Age, gender, age of onset, CTQ-score, anxiety disorder, alcohol dependence and substance dependence measures were entered as predictors. Group served as outcome variable: 'good lithium responder' (G.LR) versus 'bad lithium responder' (B.LR). Table 2 presents the significance-value, the odds ratio and its confidence interval (CI) for each predictor.

The results indicate that the presence of lifetime alcohol dependence is associated with an increased chance of being in the group of bad lithium responders: Patients in the group 'lifetime alcohol dependence' are 2.37 times more likely to be a 'bad lithium responder' than patients without lifetime alcohol dependence. The effect of gender is also significant: Males are 2.20 times more likely to be a 'bad lithium responder' than females. None of the other factors seem to be related to bad lithium response.
Despite the observed effect of gender and lifetime alcohol dependence , there is no significant effect for the overall model (p = .06) and *Nagelkerke's Pseudo* R^2 = .09, indicating poor fit.

Table 2
Logistic regression results for predicting bad lithium response (Good lithium responders = 1, Bad lithium responders' = 2)

	p-value.	Odds ratio	*95% C.I.for Odds Ratio*	
			Lower	*Upper*
Gender (male=1, female= 2)	.042*	.455	.213	.972
Age	.236	.978	.944	1.014
Age of onset	.995	1.000	.960	1.042
Anxiety disorder	.192	1.735	.758	3.970
CTQ - score	.354	1.021	.978	1.065
Alcohol dependence	.030*	2.369	1.086	5.170
Substance dependence	.333	.501	.124	2.027

* $p < 0.05$
Note: R^2 = 0.09 (Hosmer & Lemeshow), 0.05 (Cox & Snell), 0.09 (Nagelkerke). Model X^2 (7, N= 283) = 13.76, p > 0.05 (p=0.06). * $p < .05$.

2. Factors predicting discontinuation of lithium treatment due to other reasons than inefficacy

To test whether the factors that are related to a more severe course are predictive for discontinuation of lithium treatment due to other reasons than inefficacy, a logistic regression was performed. Age, gender, age of onset, CTQ-score, anxiety disorder, alcohol dependence and substance dependence were entered as predictors. Group served as outcome variable: 'good lithium responder' (G.LR) versus 'Discontinuation of lithium treatment due to other reasons than inefficacy (D.OR). Table 3 presents the p-value, the odds ratio and its confidence interval (CI) for each predictor.
The results indicate that the presence of lifetime alcohol dependence is associated with discontinuation of lithium treatment due to other reasons than inefficacy: Patients with lifetime alcohol dependence are 1.94 times more likely to be in the D.OR group. None of

the other factors seem to be related to discontinuation of lithium treatment due to other reasons than inefficacy.

The effect of the overall model is not significant. This model does not predict which patients belong to the group of discontinuation of lithium treatment due to other reasons than inefficacy (p=.21) and *Nagelkerke's Pseudo R²* indicates poor fit (.04).

Table 3

Logistic regression results for predicting discontinuation of lithium treatment due to other reasons than inefficacy

	p-value.	Odds ratio	*95% C.I.for Odds*	
			Lower	*Upper*
Gender (male=1, female= 2)	.585	.865	.514	1.455
Age	.131	1.020	.994	1.046
Age of onset	.150	.980	.953	1.007
Anxiety disorder	.940	.977	.525	1.818
CTQ - score	.777	1.004	.974	1.036
Alcohol dependence	.022*	1.936	1.102	3.402
Substance dependence	.881	1.075	.418	2.763

* $p < 0.05$

Note: R^2 = .64 (Hosmer & Lemeshow), .03 (Cox & Snell), .04 (Nagelkerke). Model X^2 (7, N = 334) = 9.71, $p > .05$ (p =.21)

Differentiation within the 'D.OR' – group between discontinuation of lithium treatment due to motivational reasons and discontinuation because of side effects yields the results presented in Table 4 and 5. The two tables show the results of two logistic regressions in which age, gender, age of onset, CTQ-score, anxiety disorder, alcohol dependence and substance dependence were entered as predictors. Group served as outcome variable: G.LR versus 'discontinuation of lithium treatment due to motivational reasons' (Table 4) and G.LR versus 'discontinuation of lithium treatment due to side effect' (Table 5). The results indicate that the presence of lifetime alcohol dependence is associated with a 4.71 times more likelihood to belong to the 'discontinuation of lithium treatment due to motivational reasons' group. The overall model is significant for predicting discontinuation of lithium treatment due to motivational reasons (p = .03) and the model can explain 20 percent of the variance (*Nagelkerke's Pseudo* R^2 = .20). No association is found with discontinuation of lithium because of side effects and no effects were found for the other predicting factors in the specific subgroups. The overall model is not significant for predicting discontinuation of lithium treatment due to side effects (p = .30).

Table 4

Factors predicting discontinuation of lithium treatment due to motivational reasons

	p-value.	Odds ratio	*95% C.I. for Odds*	
			Lower	*Upper*
Gender (male=1, female= 2)	.715	1.273	.348	4.663
Age	.125	1.048	.987	1.113
Age of onset	.149	.953	.892	1.017
Anxiety disorder	.997	.000	.000	.
CTQ - score	.318	.951	.860	1.050
Alcohol dependence	.022*	4.711	1.249	17.769
Substance dependence	.317	2.595	.401	16.777

* p < 0.05

Note: R^2 = .88 (Hosmer & Lemeshow), .06 (Cox & Snell), .20 (Nagelkerke). Model X^2 (7, *N*= 259) = 15.41, *p* <.05 (*p* =.03)

Table 5

Factors predicting discontinuation of lithium treatment due to side effects

	p-value.	Odds ratio	*95% C.I. for Odds*	
			Lower	*Upper*
Gender (male=1, female= 2)	.147	.572	.269	1.218
Age	.449	1.014	.977	1.053
Age of onset	.633	1.010	.971	1.050
Anxiety disorder	.737	1.171	.467	2.932
CTQ - score	.687	1.009	.964	1.057
Alcohol dependence	.118	1.906	.849	4.280
Substance dependence	.275	.309	.037	2.543

Note: R^2 = .09 (Hosmer & Lemeshow), .03 (Cox & Snell), .06 (Nagelkerke). Model X^2 (7, *N* = 282) = 8.35, *p* > .05 (*p* =.30)

Discussion

The aim of this study was to investigate whether factors, that are related to a more severe course of bipolar disorder, will predict the efficacy of lithium BPI patients. For this purpose it was examined whether earlier onset, comorbid anxiety, comorbid alcohol dependence, comorbid substance dependence and early extreme adversity predict lithium response in a large sample of BPI patients. As expected, the current study found an association between lifetime alcohol dependence and bad lithium response. Furthermore an effect of gender is found; males are 2.20 times more likely to be 'a bad lithium responder' than females. However, earlier onset, comorbid anxiety, comorbid substance dependence and early extreme adversity were not associated with discontinuation of lithium treatment due to inefficacy or due to other reasons than inefficacy.

Alcohol dependence and lithium response

In the current study an association between lifetime alcohol dependence and bad lithium response was found, so as expected lithium may be less able to prevent relapses in patients with alcohol dependence. This is also consistent with previous studies in which alcohol dependence appears to be related to treatment resistant variants of bipolar disorder (Salloum & Thase, 2000). Additionally, the current study found an association between the presence of lifetime alcohol dependence and discontinuation of lithium treatment due to other reasons than efficacy, in particular because of motivational reasons. So the severer course in BPI patients with comorbid alcohol dependence may be related to motivational problems rather than because of purely inefficacy of lithium.

When interpreting this association between alcohol dependence and discontinuation of lithium treatment (regardless of the reason), one possibility is that discontinuation of lithium treatment causes mood episodes which in turn may lead to problematic alcohol use, for example as a form of self-medication (Bolton, Robinson, and Sareen, 2009). Other possibility is an indirect causal effect of alcohol dependence on discontinuation of lithium treatment, leading to a severe course, this is appropriate to the findings of current study regarding motivation (as descripted below). Finally, there may be a third (common underlying) factor involved, causing both alcohol dependence and discontinuation of lithium.

When zooming in on the association between alcohol dependence and discontinuation of lithium treatment due to other reasons than inefficacy, the association appeared to be specifically for discontinuation because of motivational reasons and not for discontinuation because of side effects. This relation between alcohol dependence and motivation is in line with what is known in the literature: Patients with dual diagnoses—a psychiatric disorder and a substance use disorder— are known to have more of motivational problems / noncompliance with treatment (Tsuang, Fong & Ho, 2003;

Fenton, Blyler & Heinssen, 1997). Hence, enhancing motivation for treatment in this group of patients is an essential component in treatment with lithium. The motivational problems may be partly explained by the increased risk of psychosocial problems in this group of patients. A substantial subgroup of bipolar disorder patients with alcohol dependence has serious psychosocial problems such as unemployment, financial problems and social impairment (Salloum, & Thase, 2000). It would be useful to investigate whether the patients with psychosocial problems are indeed the group in which discontinuation of lithium occurs more often.

Caution is warranted when studying bipolar patients with comorbid alcohol dependence. This group should not be considered as a homogenous group; some patients developed alcohol disorder before bipolar disorder occurred, in other cases the bipolar disorder manifested first. In these types of bipolar disorder patients different etiologies seem to be involved (Strakowski et al., 2005). The group of patients in which bipolar disorder manifested before alcohol use disorder is associated with an earlier age of onset and a worse course of bipolar disorder (Strakowski et al., 2005; Cassano et al., 2000). The current study did not differentiate between these two groups, however in order to predict optimal treatment in BPI patients with comorbid alcohol dependence, it would be useful to assess if the bad lithium responders are the patients in whom BPI manifested first.

Gender and lithium response

Gender served as a covariate in the analysis. The results show an effect of gender; males are 2.20 times more likely to be in the group that discontinued because inefficacy. It has been explored whether gender would be predictive for discontinuation of lithium treatment due to only inefficacy or also due to discontinuation for other reasons (e.g. motivational reasons and side effects). However, gender was not found to be associated with discontinuation of lithium treatment due to other reasons. This indicates that the observed gender difference exists only for discontinuation because of inefficacy and not for discontinuation of lithium treatment for other reasons.

This study is the first, that we are aware of, to report gender differences in discontinuation of lithium in patients with BPI. According to Gelenberg & Pies (2003) gender is not known to predict response to any type of medication in patients with BPI. Gender differences in clinical characteristics (e.g. comorbidity, time of first treatment, type of episodes) in bipolar disorder patients have, however, been demonstrated. This may indicate the presence of several mediating factors.

One gender differences is the prevalence of alcohol dependence in bipolar disorder patient; the prevalence is higher in men than in women (Grant et al., 2005; Frye et al., 2003; Kawa et al., 2005). This difference is reproduced in the current study. As discussed in the previous paragraph, earlier studies but also the current study show that

alcohol dependence is related to discontinuation of lithium treatment due to inefficacy and motivational reasons. So, the gender difference found for discontinuation of lithium because of inefficacy may be partly mediated by alcohol dependence. However, elaborating on this mediating effect of alcohol dependence, it is remarkable that gender does not appear to be a predictive factor for discontinuation of lithium treatment due to motivational. This could be explained by the small number of patients, only 16, in the group that discontinued lithium treatment due to motivational reasons and consequently low power. Hence, a study with a larger sample would be necessary in order to verify this result, and to examine the expected mediating effect of alcohol dependence on the found gender effect.

Several other gender differences in clinical characteristics may serve as partial mediators for the observed gender difference in lithium response. For example in a large-scale study with 1411 bipolar disorder patients (Grant et al., 2005), based on data derived from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions, women were observed to receive earlier treatment for manic episodes than men. According to the staging model, patients treated at early stages of bipolar disorder appeared to have a better response to treatment and a more favorable course of illness (Berk, Hallam & McGorry, 2007; Berk et all., 2011). In addition, Grant et al., (2005) observed that men have unipolar mania more often compared to women. There exists some evidence that unipolar manic patients tend to be less responsive to lithium compared to other BPI patients (Yazici et al., 2002). Based on this, the possible mediating effect of time between age of onset and start of lithium treatment should be examined in further research, as well as the effect of unipolar mania on gender differences.

Negative findings

Contrary to our expectations, earlier onset, comorbid anxiety, comorbid substance dependence and early extreme adversity were not associated with bad lithium response or discontinuation of lithium treatment because of other reasons than efficacy.

Perhaps these results may be explained by methodological shortcomings. As described in the method section, the variable alcohol dependence and the variable substance dependence are composed of two combined measurements; for part of the cases the MINI was used, in other cases alcohol dependence and substance dependence were derived from data obtained with the CIDI. However, the correlation between both measurement methods appears to be moderate for the measurements of alcohol dependence and high for the measurements of substance dependence in current study, indicating no problems in terms of convergent validity. Moreover, both measures have

the same measuring pretention and the psychometric quality of both measures is more than sufficient (Sheehan et al., 1997; Andrews & Peters,1998).
The absence of predictive value of anxiety disorders on lithium discontinuation because of inefficacy, could be explained by a power problem: At first glance, the percentage of patients with an anxiety disorder is much higher in the group of bad lithium responders, than in all other groups: 34% versus 23%, however this difference is not significant. Perhaps the absence can be explained by the sample size; although the total sample may be classified as large, the subgroups are relatively small. There are 252 patients in the good lithium responders group, while there are 35 in the group bad lithium responders. It cannot be ruled out that there would have been an effect for anxiety disorders in case a larger sample size was used. Therefore, a future study with a larger sample size, would be valuable.
Nonetheless, the finding of the absence of predictive value for anxiety disorders on lithium discontinuation is less surprising and more in line with the literature when releasing the severity profile and concentrating on the motivational. It was found that the relationship between alcohol dependence and discontinuation of lithium is related to motivational reasons for a large part. Patients with comorbid alcohol use disorder are known to have high levels of motivational problems / noncompliance with treatment whereas in patients with comorbid anxiety disorders such a relationship is not evident, based on a meta-analysis by DiMatteo, Lepper, & Croghan (2000).

The negative results suggests that an model drafted on the basis of a severity profile does not have predictive value on lithium response. Except for alcohol dependence, none of the factors that are related to a severe course (early onset, comorbid anxiety, early extreme adversity and comorbid substance dependence) does predict discontinuation because of inefficacy. This makes further research based on other profiles, as motivation, necessary. Hence, more clarity is required about the by patients experienced shortcomings of lithium and about the reasons for discontinuation of lithium. The lithium questionnaire lacks the ability to collect specific information. Therefore it would be useful to extend the lithium questionnaire with questions and response options in order to obtain more specific information. For example; is the inefficacy mainly reported as the inadequate management of mania or rather the inadequate management of depression or during maintenance therapy? And what about the other reasons for discontinuation of the lithium treatment? What is covered by the motivational problems? What is the nature of these problems? Answering these questions would lead to more clarity about the reasons for discontinuation of lithium treatment. This would make more precise research in search of factors associated with discontinuation of lithium treatment possible.

In conclusion, this study found that the presence of lifetime alcohol dependence is associated with an increased risk of discontinuation because of inefficacy. None of the other factors of the severity profile i.e. earlier onset, comorbid anxiety, comorbid substance dependence and early extreme adversity seem to be related to bad lithium response. The severity profile therefore appears to be an unusable basis for drafting a predictive model for discontinuation of lithium treatment. Furthermore, it was found that gender has predictive value on discontinuation of lithium treatment due to inefficacy. This may be partly mediated by the effect of comorbid alcohol dependence, since gender differences have been demonstrated in alcohol dependence, there may be other mediating factors involved. Interestingly, in the current study alcohol dependence is as well associated with the discontinuation of lithium treatment due to motivational reasons. This may reflect a influence of motivation in lithium treatment in BPI patients. Therefore, strictly monitoring motivation for treatment and enhancing compliance should be an essential component in treatment with lithium, especially in patients with comorbid alcohol dependence.

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