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Long-Term Outcome after Lithium Augmentation in Unipolar Depression: Focus on HPA System Activity

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Key Words

Dexamethasone/corticotrophin-releasing hormone test · Long-term outcome · Major depression · Neuroendocrinology · Prediction of relapse · Recurrence

Abstract

Background: Lithium augmentation is a first-line strategy for depressed patients resistant to antidepressive therapy, but little is known about patients' subsequent long-term course or outcome predictors. We investigated long-term outcomes of unipolar depressed patients who had participated in a study on the effects of lithium augmentation on the hypothalamic-pituitary-adrenocortical system using the combined dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test. **Methods:** Twelve to 28 months (mean 18.6 ± 4.6 months) after lithium augmentation, 23 patients were assessed with a standardized interview, of which 18 patients had complete DEX/CRH test results. Relapse was diagnosed by DSM-IV criteria (Structured Clinical Interview for

DSM-IV; SCID I). **Results:** Only 11 patients (48%) had a favorable follow-up, defined as absence of major depressive episodes during the observation period. Patients with a favorable and an unfavorable course did not differ in clinical or sociodemographic parameters, endocrinological results or continuation of lithium. However, fewer previous depressive episodes tended to correlate ($p = 0.09$) with a favorable course. **Conclusion:** Results from studies using the DEX/CRH test to predict relapse in depressed patients treated with antidepressants were not replicated for lithium augmentation. Our finding could reflect the elevation of DEX/CRH results by lithium, independent of clinical course. Limitations of the study are its small sample size, the heterogeneous clinical baseline conditions and the lack of lithium serum levels. The fact that lithium continuation did not predict the course might be related to the difference between the efficacy of lithium in controlled studies and its effectiveness in naturalistic settings.

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Introduction

Lithium augmentation was first described by de Montigny et al. [1]. Its clinical evidence and hypotheses on its mode of action have been reviewed repeatedly [2, 3]. Lithium augmentation has been recommended as a first-line strategy for depressed patients not responding to standard antidepressant therapy in evidence-based treatment guidelines [4]. Randomized placebo-controlled trials have shown the efficacy of lithium augmentation for different classes of antidepressants [5–7]. A recent meta-analysis of 10 randomized placebo-controlled trials confirmed that lithium is an effective augmentation strategy in patients with depressive disorders, with an odds ratio of 3.11, a number needed to treat of 5 and a significantly higher rate of responders compared to placebo treatment (41.2 vs. 14.4%) [8]. However, none of the placebo-controlled studies reported data that had been gathered for longer than 6 weeks. Therefore, little is known about the medium and long-term course of depressed patients who underwent lithium augmentation.

Treatment-refractory depressed patients have a particularly high risk of relapse [9, 10]. Because lithium augmentation is typically applied to this group of patients, more valid data on the predictors of the long-term course of lithium-augmented patients under naturalistic conditions are needed.

Nierenberg et al. [11] retrospectively investigated the course of 66 patients who had been treated with lithium augmentation in a naturalistic design. After a mean follow-up of 29 months, a positive long-term outcome correlated only to a fast and positive response to the initial lithium augmentation. Shergill et al. [12] evaluated the course of 53 patients out of a sample of 76 patients from 2 controlled studies on lithium augmentation 4–8 years after treatment. Seventy-two percent of the sample had a good course (defined as the absence of hospitalization due to affective illness), which correlated with an absence of previous hospitalizations, a smaller degree of 'endogeneity' and with non-continuation of lithium medication.

We reported results from a double-blind placebo-controlled study of lithium augmentation in continuation therapy with a double-blind phase of 4 months and a subsequent open-label phase of 6 months [13, 14]. In the latter trial, patients taking an antidepressant combined with lithium had a significantly lower risk of relapse than patients taking an antidepressant combined with placebo.

Studies available on the follow-up of acute lithium augmentation do not examine social stressors as medi-

tors of relapse, nor do they explore endocrinological variables, both of which are important as the correlation of long-term course with social variables [15–17] and endocrinological parameters [e.g. 18, 19] is indicated by a wide variety of studies.

The hypothalamic-pituitary-adrenocortical (HPA) system is putatively the best-studied biological system in affective disorders with the development and course of depression being linked to central regulation impairment of the HPA system [20, 21]. Previous research has established the dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test as the most sensitive challenge test for identifying HPA dysfunction [21]. The procedure of the DEX/CRH test has been described in detail elsewhere [22].

Using the combined DEX/CRH test, Zobel et al. [18, 19] examined 74 inpatients who had recently recovered from a major depressive episode after antidepressant pharmacotherapy. A higher cortisol reaction in the DEX/CRH test predicted a relapse in the 6-months follow-up. Furthermore, in a comparison of the DEX/CRH test at hospital admission with a test performed shortly before discharge (after successful acute treatment), patients with a later relapse ($n = 13$) showed an increase in cortisol response. In contrast, the 61 patients who remained stable during follow-up displayed a decrease in the mean cortisol response.

In particular, we investigated the relationship between the HPA system and the clinical course during the observation period. In the current study, we performed a follow-up investigation of 30 patients who were treated with lithium augmentation within a study investigating the acute outcome of lithium augmentation and endocrinological correlates ('initial study'). Eleven patients responded within the initial study according to predefined criteria [decrease in Hamilton Depression Rating Scale 17-item score (HDRS-17) $\leq 50\%$ and total HDRS-17 score < 10]. Both responders and non-responders showed a significant increase in cortisol and adrenocorticotrophic hormone (ACTH) response from the first to the second DEX/CRH test.

In the current study, we evaluated the course of the illness over a follow-up period with a mean length of 18 months under naturalistic conditions, and tried to identify clinical, therapeutic and psychosocial variables, as well as important life events, during the follow-up period as outcome predictors. Results of the acute treatment phase (4 weeks), which focused on the HPA system, have been published elsewhere [22, 23].

Method

Subjects

Twenty-three of the 30 patients of the initial study (77%) were available for the follow-up investigation. Six patients could not be interviewed because they had moved abroad ($n = 2$) or to an unknown location ($n = 4$); 1 patient declined participation in the follow-up interview. Seventeen of the 23 patients were interviewed face-to-face, and the other 6 by telephone.

In the initial study, 30 unipolar depressed patients, who were refractory to a trial with an antidepressant (minimum dosage of 150 mg imipramine equivalent) of at least 4 weeks, were subsequently treated with lithium augmentation. All patients were diagnosed as suffering from a major depressive episode according to DSM-IV (confirmed by SCID I; German version [24]). In the initial study, a combined DEX/CRH test was performed the day before lithium augmentation was started, and the test was repeated 2–4 weeks later. Response was determined by weekly ratings with the HDRS-17 [25].

The study protocol was approved by the Ethics Committee of the Medical Faculty of the Freie Universität Berlin.

Data Collection

All eligible patients of the initial study were contacted by phone or mail and examined in a standardized face-to-face interview no less than 1 year after the end of the initial study. Current lithium treatment was not an inclusion criterion for the follow-up study. All those participating in the present follow-up investigation received a financial reimbursement of EUR 25. If a face-to-face interview was not possible, a telephone interview was carried out.

After the patients had given written consent (none refused), additional information was obtained from the charts and reports of in- and outpatient clinics or private practices where they had been treated during the follow-up period.

The following information was collected:

- Clinical course of the affective disorder or any other psychiatric disorder. For all phases of a possible psychiatric illness during the follow-up period, the SCID I interview was applied to confirm diagnosis.
- Course of treatment during the follow-up period with regard to in- and outpatient treatment, psychotherapy and pharmacotherapy; with special attention to information about continuation or withdrawal of the lithium medication.
- Suicide attempts and suicides.
- Present social situation: living circumstances, financial situation, occupational status.
- Non-psychiatric diseases and treatment during the follow-up period.
- Important life events, systematically evaluated with the List of Threatening Events Questionnaire [26].
- Mental status and depression severity (HDRS-17).

Further parameters ascertained during the initial study were also taken into the analyses: the $ACTH_{peak}$ and $cortisol_{peak}$ values in the DEX/CRH test during lithium augmentation and the difference in $cortisol_{peak}$ (change $cortisol_{peak}$) between the first (prior to lithium augmentation) and the second (under ongoing lithium augmentation) DEX/CRH test.

Outcome Criterion

The clinical course was classified as favorable if, according to DSM-IV, no major depressive episode occurred during the follow-up period. If a major depressive episode occurred (relapse or recurrence), the course was classified as unfavorable. Accordingly, patients with no remission throughout the entire follow-up period ($n = 3$) were also classified as having an unfavorable outcome. Although this strategy implies some obvious methodological shortcomings, for reasons of statistical power we decided not to split the sample into 3 different groups. The follow-up period was defined as the time span from hospital discharge (after the end of the initial study) to the date of the follow-up investigation. In addition, univariate and logistic regression analysis for only the first 12 months of follow-up was performed to assess all subjects (with varying follow-up intervals ranging from 12 to 28 months) for a comparable period of time.

Statistical Analysis

Univariate differences between patients with a favorable outcome and those with an unfavorable outcome were assessed using the Mann-Whitney U test or, in the case of dichotomous variables, using Fisher's exact test. In order to confirm the univariate results, a logistic regression analysis (simultaneous inclusion) with the demographic, illness- and treatment-related variables and a second logistic regression analysis with the endocrinological parameters were performed. The following parameters were included in the first analysis to consider the major factors that contribute to treatment outcomes: age and gender, duration of index episode until start of lithium augmentation, number of previous depressive episodes, response status in the initial lithium augmentation study and the duration of continued lithium intake during the follow-up period. Because the individual follow-up periods varied, the duration of continued lithium intake during the follow-up period was expressed as the ratio of the duration of lithium intake during the follow-up period (in weeks)/duration of the follow-up period (in weeks). The second analysis included as potential predictors: the change $cortisol_{peak}$ and change $ACTH_{peak}$ between the first DEX/CRH test and the second DEX/CRH test, as well as the peak cortisol and ACTH concentrations ($cortisol_{peak}$; $ACTH_{peak}$) in the second DEX/CRH test.

Results

Study Population

Figure 1 shows the changes in study population from the initial study to the current one. The 23 patients interviewed (12 female and 11 male) were aged 50.8 ± 16.3 years at the time of the follow-up interview. On average, they had 2.6 ± 3.0 depressive episodes and 1.4 ± 1.4 psychiatric hospitalizations prior to the index episode (i.e. initial study). In the initial study, 9 of the 23 patients had been classified as responders and 14 as non-responders to lithium augmentation. The follow-up investigation was performed at an average of 18.6 ± 4.6 months (range: 12–28) after termination of the initial study.

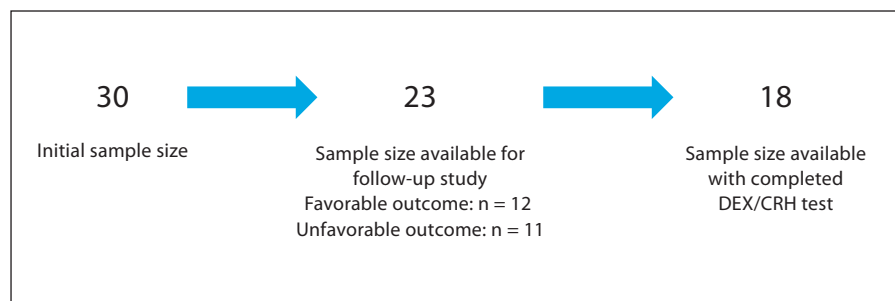


Fig. 1. Availability of the study population from the initial study for the follow-up investigation.

Outcome during the Follow-Up Period

Eleven of the 23 patients (48%) experienced no major depressive episodes (favorable outcome) and 12 (52%) had an unfavorable outcome during the follow-up period.

Of the 12 patients with an unfavorable course, 2 had a relapse within the first 6 months after recovery, and 6 suffered from a later recurrence. Among the latter, 2 patients actually had 2 depressive recurrences. Three of the 12 patients (non-responders in the initial study) developed a chronic course of the depression and did not reach remission within the entire follow-up period, although they had been discharged from the psychiatric hospital. One patient exhibited a manic episode 13 weeks after the end of the initial study and a following depressive recurrence 30 weeks later. Subsequently, his diagnose was changed to bipolar disorder. The depressive relapses and recurrences occurred in a wide time span ranging from 8.5 to 80.0 weeks after the end of the initial study (mean: 46.4 ± 28.2 weeks).

Nine of the 12 patients with an unfavorable course had to be re-hospitalized during the follow-up period, 4 of them twice. Two of the 12 had attempted suicide (wrist cut and intoxication with tablets, respectively), but no patient had died from suicide.

Demographic, Illness and Treatment-Related Variables

According to the univariate analyses, patients with a favorable and an unfavorable outcome did not differ in a statistically significant way with regard to demographic, illness or treatment-related variables (table 1). Age, gender, age at first depressive episode and duration of the index episode prior to lithium augmentation were not significantly different. It is noteworthy that the course experienced by responders to the initial lithium augmentation was not better during follow-up than that of non-responders. The duration of continued lithium intake

during the follow-up period (in percent of the duration of the individual follow-up period) was comparable in both groups (29%). During 54% of the time of the follow-up period, patients were taking at least 1 antidepressant (no significant group difference). A similar number of patients with favorable (55%) and unfavorable follow-ups (58%) underwent psychotherapy. Thirteen of the 23 patients had experienced at least 1 life event according to the List of Threatening Events Questionnaire; 6 with a favorable and 7 with an unfavorable follow-up. In detail, 6 life events were the death of a relative, 3 a severe somatic illness, 3 the ending of a relationship, 2 a severe financial crisis, 2 a severe familial or partnership conflict and 2 patients had been victims of a crime.

Patients with a favorable course, however, tended to have fewer previous depressive episodes (1.8 ± 2.9) compared to those with an unfavorable course (3.2 ± 3.0 ; $p = 0.09$, univariate analysis). Not surprisingly, the patients with an unfavorable follow-up had a significantly higher HDRS-17 score at the interview compared to the stable group ($p = 0.02$).

Endocrine Variables

Five of the 23 patients had refused re-assessment with the combined DEX/CRH test in the initial study; therefore, full information on the HPA system parameters was only available for 18 patients (9 with a favorable and 9 with an unfavorable course). As shown in table 2, $ACTH_{peak}$ and $cortisol_{peak}$ values in the DEX/CRH test during ongoing lithium augmentation appeared to be higher in patients with a subsequent unfavorable course compared to patients with a favorable course ($ACTH_{peak}$: 38.7 ± 34.6 vs. 32.6 ± 29.1 pg/ml; $cortisol_{peak}$: 103.3 ± 77.5 vs. 71.6 ± 39.8 ng/ml). However, differences were not statistically significant. Apart from the peak values, Δ values (peak value minus baseline value) and area under the curve (AUC) values were also used to quantify the

Table 1. Demographic, illness and treatment-related variables of 23 patients with major depressive disorder who were followed up after lithium augmentation

	Total (n = 23)	Favorable course (n = 11)	Unfavorable course (n = 12)	Univariate p values
Gender (female:male)	12:11	6:5	6:6	1.0
Age at follow-up, years	50.8 ± 16.3	48.8 ± 15.8	52.6 ± 17.2	0.53
Length of follow-up interval, months	18.6 ± 4.6	17.3 ± 4.9	19.8 ± 4.2	0.13
Responders to lithium augmentation in the initial study	9	5	4	0.68
Number of previous depressive episodes	2.6 ± 3.0	1.8 ± 2.9	3.2 ± 3.0	0.09
Number of previous psychiatric hospitalizations	1.4 ± 1.4	1.0 ± 1.2	1.8 ± 1.5	0.21
Age at onset of mood disorder, years	37.7 ± 16.5	37.6 ± 17.0	37.9 ± 16.8	0.93
Duration of index episode up to start of lithium augmentation, weeks	44.9 ± 50.1	46.4 ± 56.2	43.6 ± 46.5	0.98
HDRS-17 prior to lithium augmentation	20.3 ± 4.0	19.0 ± 3.6	21.4 ± 4.1	0.13
HDRS-17 at the beginning of the follow-up period	12.7 ± 7.4	11.4 ± 7.0	13.9 ± 8.0	0.45
HDRS-17 at follow-up	8.5 ± 5.9	5.2 ± 3.8	11.5 ± 6.0	0.02
Duration of continued lithium intake, weeks	22.5 ± 29.4	18.9 ± 27.0	25.9 ± 32.3	0.65
Ratio of duration of continued lithium intake/duration of follow-up	0.29 ± 0.38	0.29 ± 0.41	0.29 ± 0.37	0.93
Ratio of duration of intake of at least 1 antidepressant/duration of follow-up	0.54 ± 0.33	0.60 ± 0.36	0.49 ± 0.31	0.46
Specific psychotherapy during the follow-up period	13 (57)	6 (55)	7 (58)	1.0
Life events during the follow-up period ¹	13 (57)	6 (55)	7 (58)	1.0
Working	9 (39)	6 (55)	3 (25)	0.21
Living alone	11 (48)	4 (36)	7 (58)	0.41

Data presented as means ± SD or numbers (percentages). Favorable course = No major depressive episode according to DSM IV (SCID I validated) at any time during the follow-up period. For dichotomous variables, Fisher's exact test was used to calculate the p values, for all other variables the Mann-Whitney U test was used.

¹ Assessed by the List of Threatening Events Questionnaire.

Table 2. ACTH and cortisol responses to the combined DEX/CRH test before and after lithium augmentation in patients with a subsequent favorable or unfavorable course

	Total	Favorable course	Unfavorable course	Univariate p values
Response in the combined DEX/CRH test before onset of LA, n	23	11	12	
ACTH _{peak} pg/ml	20.0 ± 11.1	21.4 ± 14.2	18.7 ± 7.8	0.98
Cortisol _{peak} ng/ml	63.8 ± 42.3	61.5 ± 42.6	65.9 ± 43.7	0.88
Response in the combined DEX/CRH test after onset of LA, n	18	9	9	
ACTH _{peak} pg/ml	35.7 ± 31.2	32.6 ± 29.1	38.7 ± 34.6	1.0
Cortisol _{peak} ng/ml	87.5 ± 62.0	71.6 ± 39.8	103.3 ± 77.5	0.60
Changes in endocrine response between the first and the second DEX/CRH test				
Change ACTH _{peak} pg/ml	+16.0 ± 23.4	+11.2 ± 17.3	+20.8 ± 28.6	0.67
Change cortisol _{peak} ng/ml	+27.5 ± 46.4	+12.1 ± 29.6	+43.0 ± 56.3	0.30

Data presented as means ± SD, with all p values calculated by the Mann-Whitney U test. Favorable course = No major depressive episode according to DSM IV (SCID I validated) at any time during the follow-up period. LA = Lithium augmentation.

cortisol and ACTH response to the CRH injection in the DEX/CRH test. These parameters also did not show a significant difference between patients with a favorable and with an unfavorable follow-up (data not shown in detail).

As described previously, the cortisol and ACTH response in the combined DEX/CRH test was significantly stronger during lithium augmentation compared to the pre-lithium baseline investigation [22]. This applied to patients with a favorable as well as to patients with an unfavorable follow-up. Interestingly, in the latter group this increase seemed to be more prominent. The change cortisol_{peak} was $+ 12.1 \pm 29.6$ ng/ml in the favorable and $+ 43.0 \pm 56.3$ ng/ml in the unfavorable follow-up group. However, this did not result in a significant difference. Differences between the 2 groups for ACTH response and for the Δ and AUC values were not significant either (data not shown in detail).

Logistic Regression

The logistic regression analysis with favorable/unfavorable course as the dependent variable and with a multi-step inclusion of the demographic, illness and treatment-related parameters mentioned above ($n = 23$) did not reveal a significant model. Nor did the second logistic regression analysis with the endocrinological parameters ($n = 18$) yield a significant model.

Outcome in the First 12 Months of Follow-Up

The follow-up interval of the patients ranged from 12 to 28 months. Accordingly, subjects with a longer follow-up period were at a greater risk of recurrence. Although the length of the follow-up interval was comparable between patients with a favorable and with an unfavorable course (17.3 ± 4.9 and 19.8 ± 4.2 months, respectively), we repeated all univariate and logistic regression analyses, restricting them to the first 12 months of the follow-up period (data not shown in detail). Four patients (all female) were stable in the first 12 months, but experienced a later recurrence. Hence, in this analysis 15 patients were classified as having a favorable and 8 as having an unfavorable outcome.

With regard to statistical significance, results were not different compared to the analysis of the full follow-up interval. Interestingly, gender and living alone appeared to be different between patients with a favorable and an unfavorable course. Six out of 11 men, but only 2 out of 12 women had an unfavorable course in the first 12 months (univariate $p = 0.089$; logistic regression analysis: $p = 0.057$). In addition, 6 out of 11 patients who lived

alone, but only 2 out of 12 who did not, suffered from a major depressive episode in the first year of the follow-up interval (similarly, univariate $p = 0.089$; logistic regression analysis: $p = 0.057$).

Discussion

We present a follow-up investigation of a study ('initial study') of unipolar depressed patients who were resistant to a treatment trial with an antidepressant of at least 4 weeks and who had subsequently been treated with lithium augmentation. Twenty-three of 30 (77%) of the initial study population was recruited for the follow-up investigation. This figure is in range of the recruiting rates of other studies dealing with lithium augmentation follow-up, i.e. 70% [12] or 88% [11]. Neuroendocrine data were available for 18 patients.

The outcome of the follow-up period is sobering. More than half of the patients (52 %) had an unfavorable course according to the predefined criteria, with no difference in clinical, sociodemographic or endocrinological parameters nor with regard to the duration of continuation treatment with lithium compared to patients with a favorable course. However, it should be taken into account that the patients of this study are a selected group of severely ill patients: all patients had been hospitalized for the treatment of the index episode, which in turn had lasted for a considerably long period of 44.9 ± 50.1 weeks on average, and by definition the patients had been refractory to at least 1 trial of antidepressive pharmacotherapy prior to lithium augmentation. Therefore, and in view of the small sample size, this result cannot be generalized. Furthermore, the results reflect a course under naturalistic conditions. Not all patients may have received optimal treatment during the follow-up period, and some received no treatment.

An unexpected result of the study is that neither response to initial lithium augmentation nor continued intake of lithium correlated with a favorable outcome during the follow-up period. This result is in line with findings on the long-term course after a major depressive episode and the intake of antidepressants [16], but is in contrast to the well-established efficacy of lithium to prevent affective relapses in controlled and naturalistic studies [27] which was previously confirmed for the continuation therapy phase of lithium augmentation [13, 15]. However, a discrepancy between the efficacy in controlled studies and the effectiveness in the naturalistic use of lithium has been repeatedly discussed [28–34].

This incongruity may contribute to the outcome in the study presented here. If so, the results do not question the use of lithium, but rather emphasize the need to improve the naturalistic outpatient care.

Neither the demographic nor clinical variables were correlated with the outcome during the follow-up period. This result conforms with previous studies on this topic [11, 12]. Patients with an unfavorable outcome displayed a trend towards a history of more depressive episodes. This trend is not surprising and probably reflects a more active course of the disease in this group. Living alone has been reported to be associated with a higher prevalence of depression [35]. With restriction to the first year of the follow-up period, our sample showed a non-significant trend for a worse course for patients who lived alone.

The endocrinological results of the combined DEX/CRH test also did not predict the course during the follow-up period. Comparable to the study of Zobel et al. [18, 19] in antidepressant-treated patients, the patients with an unfavorable follow-up had higher cortisol values in the second DEX/CRH test. The effect size of the difference in cortisol_{peak} response was calculated as 0.67, which is between the conventions of a medium and large group effect [36]. However, we failed to demonstrate a significant group difference. This might be due to the small sample size or to the lithium comedication. Furthermore, Zobel et al. [18, 19] only investigated the continuation treatment phase (6 months). However, when restricting the analysis of our study to a 6-month follow-up, the endocrinological results do not differentiate between patients with favorable or unfavorable follow-up (data not shown).

A substantial difference of our study to previous studies which show the association of a favorable long-term outcome with normalization of HPA system activity is that our sample was investigated under the conditions of a lithium challenge. Lithium medication could influence the predictive value of the DEX/CRH test. We have shown in the 'initial study' that lithium application results in an elevation of the DEX/CRH test response compared to baseline and does not reflect clinical response [22]. This effect of lithium has been described to be independent of psychopathological state or improvement. The relapse predictive value of the DEX/CRH test might therefore not be generalizable to antidepressant-treated patients with lithium comedication. Replication of our study with a larger number of subjects would be worthwhile. We also see the need for larger long-term follow-up studies of lithium-augmented patients under naturalistic conditions with regard to factors that modify the long-term course.

It is generally worth noting that after the initial findings suggesting a correlation of DEX/CRH test findings and clinical course a lack of relationship between the restoration of HPA system dysfunction and acute treatment response has also been reported [37]. Single substances, such as lithium in this study, may also 'break the rules' as has been reported for mirtazapine [38].

Aside from the sample size, there are several other limitations of the study. Due to the study design, subjects started the follow-up interval under different clinical conditions: either depressed or remitted. Furthermore, lithium was prescribed in a naturalistic non-standardized manner. Exact lithium doses and serum levels were not documented. Reliable data on the appropriateness or length of lithium treatment during the follow-up period are not available, and may have affected the clinical results.

In conclusion, the study results indicate that substantial effort needs to be made to stabilize the course of depressed patients after lithium augmentation in the acute treatment phase. Although we cannot replicate the relapse predictive findings from patients treated without lithium, it seems noteworthy that, as in other studies, we find patients with an unfavorable course after treatment of a major depressive episode to have higher cortisol and ACTH values in the combined DEX/CRH test.

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