Are Illness Concepts a Powerful Predictor of Adherence to Prophylactic Treatment in Bipolar Disorder?

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Background: Predicting and preventing premature discontinuation of medication would substantially improve prophylactic treatment of bipolar disorder. Patients' concepts regarding illness proved to have an impact on noncompliance in a retrospective study of patients with affective or schizoaffective illness treated with lithium. The present study is the first to prospectively investigate the influence of illness concepts on adherence of bipolar patients to different medications.

Method: 171 bipolar patients (DSM-IV) were randomly assigned to receive either lithium (N = 86) or carbamazepine (N = 85) and observed for a maintenance period of 2.5 years (Multicenter Study of Affective and Schizoaffective Psychoses). The total score and 7 dimensions of illness concepts and treatment expectations of the Illness Concept Scale (ICS) were calculated for 141 patients with completed questionnaires and used to predict time to dropout (Cox regression). Analyses were corroborated by further multivariate analyses with sex, age, and premorbid personality as covariates.

Results: With lithium treatment, but not carbamazepine treatment, the total ICS score at study entry was associated with a longer time to study dropout ($p = .001$ and $p = .224$, respectively). The relevant ICS subscales affecting time to dropout in patients treated with lithium were trust in medication, trust in the treating physician, and absence of negative treatment expectations. Multivariate analyses suggested that the impact of these variables on adherence to lithium was largely independent of sociodemographic, clinical, and psychological variables. Our data indicate that the stronger impact of illness concepts with lithium as compared with carbamazepine treatment might be related to the drugs' different side effect profiles.

Conclusion: As trust in drug treatment and trust in the treating physician had a clear impact on adherence to prophylactic lithium, patients' illness concepts and treatment expectations might be promising targets for psychoeducation and psychotherapy in the treatment of bipolar disorder.

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According to Cade, the first manic patient successfully treated with lithium "was soon back working happily at his old job. However, he became more lackadaisical about his medicine and finally ceased taking it."[1(p350)] Eventually, the patient became "irritable and erratic," stopped working, and had to be readmitted to the hospital. Since Cade reported this case in 1949, thousands of lithium patients have suffered from clinical consequences of noncompliance followed by recurrence and its possible consequences such as vocational and financial crises, interpersonal chaos, and suicide.[2–4] Moreover, clinical research has found that abrupt discontinuation of lithium might trigger psychotic states.[5–7] Several authors have concluded that nonadherence to medication is probably the most limiting factor in long-term treatment with lithium.[2,3,8–12]

Despite the commonness and the severely damaging sequelae of treatment discontinuation, poor adherence to prophylactic treatment of bipolar disorder is still much understudied.[2,13–16] Nonadherence is a complex phenomenon associated with a multitude of factors related to the illness, to treatment, to the physician, and to the patient.[17] Overviews of variables that have been found to be associated with nonadherence in bipolar disorder have been published by Lingam and Scott,[16] Keck et al.,[10] and Goodwin and Jamison.[2]

The present article focuses on patients' concepts and expectations regarding illness and therapy. As it is the patient who finally decides whether to continue taking medication, it must be assumed that the patient's illness concepts are the proximate determinants of this decision[13]; this has been supported by studies of patients' reasons for nonadherence.[17] Nonadherent patients reported missing their "highs" or being "bothered by the idea that moods are controlled by medication"[17(p868)] and tended to

deny their illness.[10] The coping strategy of denial was found to undermine medication adherence.[18] The major role of patients' illness concepts with regard to noncompliance is underscored in a study by Schumann et al.,[15] who used the Lithium Attitudes Questionnaire[19] to directly investigate the influence of treatment-related attitudes on adherence to long-term lithium treatment. The study clearly shows a strong impact of illness concepts such as denial of effectiveness of lithium. The study was, however, retrospective in nature, and the authors recommend replication within a prospective design. A further limitation is that the study comprised different diagnostic groups including unipolar depressive, bipolar, and schizoaffective patients. It would also be desirable to test the extent to which the findings of Schumann et al.[15] can be extended to other mood stabilizers such as carbamazepine, valproate, or lamotrigine.[20]

The present study is the first to prospectively investigate the impact of illness concepts on adherence to mood-stabilizing treatment. Random assignment of patients to either lithium or carbamazepine treatment allowed us to determine the extent to which the impact of illness concepts is specific to lithium. Variables such as age, sex, premorbid personality, side effects, and number of previous episodes that were hypothesized to be related to patients' illness concepts were included in both univariate and multivariate analyses to clarify the relationship between illness concepts and nonadherence.

METHOD

Study Design

The general study design, recruitment process, subject selection, and clinical assessments of the Multicenter Study of Affective and Schizoaffective Psychoses have been described in detail previously.[21–24] To summarize briefly, patients in need of prophylactic treatment who were between the ages of 18 and 65 years were recruited while hospitalized in one of the 9 German study centers (Aachen, Berlin, Düsseldorf, Heidelberg, Lübeck, Munich, Münster, Tübingen, and Würzburg). In these centers, patients with a bipolar affective or schizoaffective episode (ICD-9) were screened during hospitalization and entered the study if they fulfilled the following criteria: current episode of an affective or schizoaffective disorder according to ICD-9 (296.2–296.4, 296.7), at least 1 additional episode during the last 4 years for bipolar disorder or the last 3 years for schizoaffective disorder, no prophylactic treatment immediately before the current episode, no diagnosis of alcohol or drug abuse (current), no contraindication against one of the study medications, age between 18 and 65 years, and provision of informed consent. Approval for the study was obtained from a board established by the Federal Ministry of Research and Technology. The study protocol was developed based on Declaration of Helsinki and Good Clinical Practice guidelines.

As the study assessed the efficacy of maintenance (not continuation) treatment, patients entered the study after recovery from the index episode (Global Assessment Scale [GAS] score > 70 for at least 2 weeks within 6 months after discharge). Patients were randomly assigned to receive either lithium or carbamazepine as study medication. Randomization was concealed from the study centers using lists that were kept in the coordinating center. At the time of randomization, the treating physician was notified by phone of the treatment group allocation of the respective patient. After random assignment to prophylactic treatment, the study patients were treated in an outpatient setting during a maintenance phase of 2.5 years. The design of the study was nonblind. Psychotropic comedication was avoided during the maintenance phase; however, if use of concomitant medication was judged to be inevitable, it was accepted and documented. A polydiagnostic approach was used, in which patients were diagnosed not only according to ICD-9 but also according to DSM-III-R using the Structured Clinical Interview for DSM-III-R Mental Disorders (SCID) and Research Diagnostic Criteria. This article summarizes the results for patients with DSM-III-R–defined bipolar affective disorder using terminology in accordance with the redefinition of diagnostic criteria in DSM-IV (see Greil et al.[25]).

In the case of study noncompletion (dropout), a detailed standardized protocol for recording the dropout reasons was completed in the study center by the physician. For the purposes of the present article, the various reasons for dropout were summarized in 2 categories: dropouts due to noncompliance and dropouts due to other reasons (such as adverse events or inefficacy of therapy). A dropout as defined in the context of the present article may have occurred before or after reoccurrence of an affective episode.

Adverse events were assessed regularly by the physician using a checklist for 59 symptoms known to occur frequently with lithium or carbamazepine. This checklist was supplemented by reporting of further unwanted side effects by the patient. All items were rated on a 4-point scale ranging from 0 (nonexistent) to 3 (prominent) and added up to the total side effect score. To assess patients' subjective impairment due to medication, a 100-mm visual analogue self-rating scale was used that ranged from "My medication does not cause any disturbing side effects" to "I feel substantially impaired by the side effects of my medication" (for details, see Greil et al.[26]). During the first 3 months of the observation period, side effects were assessed at 4-week intervals. Thereafter, the regular interval was 8 to 12 weeks.

Illness concepts were assessed at study entry using the Illness Concept Scale (ICS).[27–29] Patients were in stable condition (GAS score > 70 for at least 2 weeks) when ill-

Table 1. Sociodemographic, Clinical, and Psychological Variables in Bipolar Patients at Study Entry

Variable	Lithium			Carbamazepine		
	All (N = 86)	Completers (N = 64)	Dropouts (N = 22)	All (N = 85)	Completers (N = 46)	Dropouts (N = 39)
Diagnostic subgroup, bipolar I, %	67	71	55	66	63	69
Sex, female, %	55	55	55	58	57	59
Age, mean ± SD, y[a]	41 ± 13	43 ± 14	32 ± 10	39 ± 13	40 ± 12	38 ± 15
Manic or mixed index episode, %	31	36	18	23	26	19
Presence of mood-incongruent delusions at index episode, %	26	22	36	22	30	13
No. of previous episodes, mean ± SD	3.3 ± 2.3	3.5 ± 2.6	2.7 ± 1.5	3.1 ± 2.2	2.2 ± 1.4	3.9 ± 2.6
GAS score at beginning of study, mean ± SD	79 ± 10	80 ± 9	75 ± 11	79 ± 10	81 ± 9	77 ± 10
Psychiatric comorbidity (mostly lifetime diagnosis of anxiety disorders and substance abuse), %	16	13	27	16	20	13
Munich Personality Test score, mean ± SD						
Neuroticism	10.1 ± 5.3	10.2 ± 5.4	9.9 ± 4.9	10.3 ± 5.6	9.5 ± 5.6	11.3 ± 5.6
Frustration tolerance	6.6 ± 3.9	6.7 ± 4.0	6.1 ± 3.5	6.9 ± 4.1	7.3 ± 4.1	6.3 ± 4.0
Extraversion[b]	11.2 ± 6.6	11.1 ± 6.5	11.3 ± 7.0	13.5 ± 5.7	13.5 ± 6.3	13.4 ± 4.9
Rigidity	10.0 ± 4.4	10.4 ± 4.3	9.1 ± 4.7	10.9 ± 4.6	10.2 ± 4.6	11.7 ± 4.5
Schizoidia	3.0 ± 1.6	2.9 ± 1.6	3.1 ± 1.6	2.7 ± 1.9	2.5 ± 1.7	3.0 ± 2.1

[a]p = .03 (Wilcoxon test for completer vs. dropouts: 42 ± 13 years vs. 37 ± 13). Besides age, none of the differences between completers and dropouts was significant.
[b]p = .01 (Wilcoxon test for lithium vs. carbamazepine). Besides extraversion, none of the differences between lithium and carbamazepine was significant.
Abbreviation: GAS = Global Assessment Scale.

ness concepts were assessed. The ICS consists of 7 dimensions with 29 items, each of which was scored on a 5-point Likert-type scale. The 7 dimensions, which were empirically derived by factor analyses, are as follows: trust in medication (TM), trust in the treating physician (TP), negative treatment expectations (NE), guilt (GT), chance control (CC), susceptibility (SC), and idiosyncratic assumptions (IA).[27,29] The retest reliability of the different dimensions varies from 0.73 to 0.86 within a mean interval of 66 days.[27] A total score was proposed by Linden et al.[27,29] to evaluate a patient's total illness-related attitudes with respect to compliance (total ICS score = TM + TP – NE – GT + CC + SC – IA; range, –48 to 68). An English translation of the items forming the 7 dimensions and the total ICS score is given in Appendix 1, and the ICS questionnaire is shown in Appendix 2. Besides an assessment of illness concepts, patients completed further self-rated scales such as the Munich Personality Test,[30,31] which assesses premorbid personality.

Statistical Analyses

The relations between dropout and illness concept scores were assessed using point biserial correlation. Relations involving ordinal scales (such as the subjective rating scale of impairment caused by side effects) were calculated using Spearman rank correlation. Differences of correlation coefficients for lithium and carbamazepine were tested using Fisher Z-transformation of point biserial correlation. To control for the influence of potentially confounding variables, both group comparisons and multivariate analyses were used. The Fisher exact test was used for dichotomous variables, Wilcoxon tests were used for ordinal and nonnormal continuous data, and t tests were used for normally distributed variables. Time to dropout was modeled using Cox regression. Significance testing of parameters in Cox regression models was performed using the Wald statistic. To test the influence of confounding clinical and demographic variables, stepwise Cox regression analyses with both forward and backward elimination were carried out. Time in study in the groups with a high and low total ICS score (median split) was compared using Kaplan-Meier estimates (nonparametric survival analyses). The probability of dropout was estimated with logistic regression analyses. P values lower than .05 (2-sided) were considered as statistically significant. To avoid publication of spurious results that might not hold if a different method were applied, we replicated the major results using several statistical approaches. Results were reported only if they were consistently found using all of the methods applied.

RESULTS

Study Patients

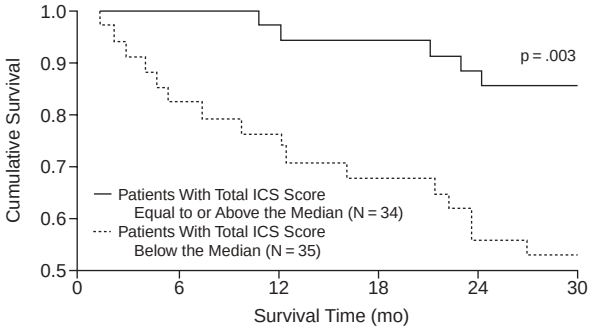
Of the 171 patients with a diagnosis of bipolar disorder (DSM-IV), 86 had been randomly assigned to lithium and 85 to carbamazepine. Mean ± SD dosages (between month 2 and study termination) were 26.8 ± 6.76 mmol/day for lithium (serum level = 0.61 ± 0.12 mmol/L) and 635 ± 190 mg/day for carbamazepine (serum level = 6.12 ± 1.27 µg/mL). As can be seen from Table 1, no significant differences between the treatment groups were found regarding clinical and sociodemographic variables including sex, age, number of previous episodes,

Table 2. Reasons for Dropout, N[a]

Reason for Dropout	Lithium (N = 86)	Carbamazepine (N = 85)
Noncompliance	12	15
Unsatisfactory efficacy of therapy	4	8
Adverse events[b]	3	8
Pregnancy	1	4
Reasons for dropout probably unrelated to treatment[c]	2	4
Total	22	39

[a]Dropout may have occurred before or after a recurrence.
[b]Lithium: acne and weight gain (N = 1), disturbances of sexual potency (N = 1), vertigo, nausea, and headache (N = 1). Carbamazepine: exanthema, lymphoma, and headache (N = 1), allergy and rash (N = 1), generalized eczema (N = 1), allergic skin reaction (N = 1), hepatopathy (N = 1), lymphoma and diarrhea (N = 1), exanthema (N = 2).
[c]For example, external circumstances such as change of residence of the patient or protocol violation by the rater.

Figure 1. Time in Study With Lithium Treatment (survival functions)



Abbreviation: ICS = Illness Concept Scale.

type of the index episode, psychiatric comorbidity, and GAS score at study entry. Regarding premorbid personality, extraversion was the only variable to differ significantly between treatment groups, with higher scores found in the carbamazepine group.

Sociodemographic and Psychological Variables

For the entire group of 171 patients, higher age was significantly related to a higher probability of treatment adherence (mean ± SD age of 42 ± 13 years among completers vs. 37 ± 13 years among dropouts, $p = .032$) and to a higher ICS score ($r = 0.18$, $p = .031$). Sex and scores on the neuroticism, frustration tolerance, extraversion, rigidity, and schizoidia dimensions of the Munich Personality Test were unrelated to both treatment adherence (see Table 1) and ICS score.

Illness Concepts and Dropout

Thirty-six percent (61/171) of the patients dropped out of the study. With carbamazepine, the risk of dropout was generally higher than with lithium (relative risk = 1.79, $p = .0067$). When the reasons for dropping out of the study were compared, no significant difference between study medications was found ($\chi^2 = 1.809$, df = 4, $p = .77$). For both medication groups, noncompliance was the most frequent reason for dropping out, followed by unsatisfactory efficacy of therapy and adverse events (Table 2).

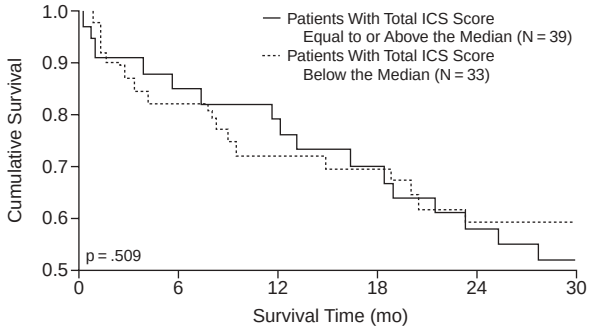
Of the 171 patients, 141 had a completed ICS questionnaire (69 in the lithium group and 72 in the carbamazepine group). No significant differences were found between patients who did and did not have a completed ICS questionnaire on any major clinical, psychological, or sociodemographic variables. The mean ± SD ICS scores were 11.9 ± 10.4 and 9.6 ± 9.1 for patients receiving lithium and carbamazepine, respectively. This difference is not statistically significant ($p = .24$, Wilcoxon test). In those treated with lithium, but not carbamazepine, high total ICS score was significantly protective against dropping out of the study ($r = 0.39$, $p = .0010$ and $r = 0.08$, $p = .51$, respectively). The difference between these correlation coefficients was statistically significant ($Z = 1.97$, $p = .049$). As illness concepts and treatment adherence were hypothesized to be related to age, sex, and personality, we clarified the relation between these variables and the risk of dropout by performing stepwise Cox regression with both forward and backward elimination. In these models, total ICS score, age, sex, and the 5 dimensions of the Munich Personality Test were used as predictors of time to dropout.

For lithium, all variables except total ICS score were eliminated from the model. Higher ICS scores were clearly associated with a longer time to dropout, i.e., longer time in treatment ($\beta = –0.088$, SE = 0.028, $\chi^2 = 10.098$, df = 1, $p = .001$). For carbamazepine, the only variable that was found to be associated with time to dropout was schizoidia: high scores of schizoidia were associated with shorter time to dropout ($\beta = 0.154$, SE = 0.072, $\chi^2 = 4.533$, df = 1, $p = .033$). These results were consistently found with both forward and backward elimination. For carbamazepine, ICS score was not found to be related to time to dropout ($\beta = –0.025$, SE = 0.020, $\chi^2 = 1.477$, df = 1, $p = .224$).

Figure 1 illustrates the impact of the ICS score on time to dropout. Of patients treated with lithium, those with a total ICS score equal to or above the median of 10 clearly remained in the study longer than those with a total score below the median (see Figure 1). For carbamazepine, no clear difference between the groups of patients with high and low ICS scores was found (Figure 2). These results were confirmed when probability of dropout was modeled using logistic regression models (p values for the predictive power of ICS scores were .003 and .509 for lithium and carbamazepine, respectively).

In sum, the results for illness concepts and personality and clinical variables indicate a clear relation between illness concepts and dropout with lithium treatment that

Figure 2. Time in Study With Carbamazepine Treatment (survival functions)



Abbreviation: ICS = Illness Concept Scale.

is not confounded by sex, age, or major psychological variables. In patients treated with carbamazepine, the risk of dropout might be related to higher scores of schizoidia.

To test whether the impact of illness concepts depended on the type of dropout, we dichotomized dropouts into those due to noncompliance and those due to other reasons. In lithium-treated patients, the correlation between total ICS score and dropout was virtually the same for both types of dropout ($r = 0.26$, $p = .030$ for dropouts due to noncompliance and $r = 0.24$, $p = .051$ for dropouts due to other reasons). The correlation in the 2 groups was also similar for carbamazepine ($r = 0.13$, $p = .29$ for dropouts due to noncompliance and $r = –0.02$, $p = .87$ for dropouts due to other reasons).

To allow for a better interpretation of the relation between total ICS score and dropout, further analyses involving the ICS subscores were performed. Among patients treated with lithium, dropout was significantly correlated to 3 subscales (trust in the treating physician: $r = –0.37$, trust in medication: $r = –0.32$, negative treatment expectations: $r = 0.28$). Among patients treated with carbamazepine, none of the subscales was significantly correlated to dropping out of the study.

Illness Concepts and Side Effects

For both drugs, the objective mean total side effect score for the 2.5 years of the observation period was found to be unrelated to nonadherence ($r = 0.05$, $p = .65$ and $r = –0.04$, $p = .74$ for lithium and carbamazepine, respectively).

To determine the extent to which illness concepts influenced the impairment caused by unwanted side effects, the correlation between total ICS score and both an objective rating of side effects and a subjective rating of impairment caused by these side effects was calculated. The ICS score was not statistically related to the objective mean total side effect score for either drug ($r = 0.01$, $p = .96$ and $r = –0.10$, $p = .40$ for lithium and carbamazepine, respectively). The subjective impairment caused by side effects, assessed with a 100-mm visual analogue self-rating scale, was negatively related to total ICS score at study entry for both drugs ($r = –0.38$, $p = .0015$ and $r = –0.41$, $p = .0004$ for lithium and carbamazepine, respectively). The results show that illness concepts may substantially influence subjective impairment caused by the drugs.

DISCUSSION

Patients' illness concepts had a clear impact on adherence to prophylactic lithium. In the context of this article, the relevant illness concepts were trust in medication, trust in the treating physician, and absence of negative treatment expectations, as these variables were most predictive of adherence to lithium. From our analyses, it can be concluded that the impact of these illness concepts is beyond the influence of sex, age, personality, and clinical variables such as number of previous episodes or psychiatric comorbidity. In contrast to the results with lithium, no correlation between the scores on the ICS and the probability of dropout was found with carbamazepine. These results clearly indicate that the effects of illness concepts with carbamazepine treatment are less pronounced than with lithium treatment.

We also examined the validity of the assumption that the higher impact of illness concepts with lithium compared with carbamazepine treatment is related to different reasons for dropping out during treatment with the 2 drugs (e.g., side effects). Indeed, we found the rate of dropout for other reasons to be distinctly higher in the carbamazepine group than in the lithium group. The impact of illness concepts was, however, the same on both types of dropouts, for lithium as well as for carbamazepine; this means that the impact of illness concepts during lithium treatment was not specific to dropouts due to noncompliance but also applied to dropouts due to other reasons such as side effects. Similarly, no impact of illness concepts during carbamazepine treatment was found, whether dropouts were due to noncompliance or not.

When interpreting these results, it is helpful to examine closely the types of adverse events that led to a dropout with lithium versus carbamazepine. For the carbamazepine group, we found that many of the adverse events represented a clear indication to discontinue carbamazepine, e.g., allergic skin reactions, lymphoma, and hepatopathy. In the lithium group, the decision to stop taking medication seemed to be more subjective considering the side effects that prompted patients to discontinue treatment, such as weight gain, acne, disturbances of sexual potency, and nausea. Accordingly, patients' trust in treatment and treatment providers might play a greater role in discontinuation of lithium compared with carbamazepine.

Pregnancies, another reason for dropout, were more frequent during treatment with carbamazepine compared with lithium (4 vs. 1). This difference could be due to a loss of efficacy of oral contraceptives or the use of less efficacious methods of contraception resulting from pharmacokinetic interactions of carbamazepine. It might also be that patients receiving lithium treatment followed more strictly the directive to avoid pregnancies during the treatment period. Since pregnant patients dropped out of the study irrespective of their illness concepts, the 4 pregnant patients in the carbamazepine group might contribute to the lower influence of patients' concepts and expectations on dropout in this treatment group.

A further explanation for the higher impact of patients' treatment expectations in the lithium group might result from the fact that lithium therapy is comparatively burdensome for the patient. Patients must have their blood lithium levels monitored regularly and observe rules in everyday life, such as avoiding certain diets and excessive sweating. Furthermore, lithium has more troublesome adverse effects, e.g., tremor, polydipsia, and polyuria, and it is known to have subtle psychic side effects in a substantial number of patients. Patients report, for example, that they feel slightly depressed[32] or less creative.[2] All in all, lithium therapy appears to be more inconvenient for the patient than carbamazepine therapy and therefore requires of patients greater willingness and positive attitudes such as trust in medication and physicians to maintain the therapy for a long time.

The findings reported in this article stem from a controlled study. Care was taken to avoid treatment with one of the study medications during the index episode and to avoid rapid withdrawal of any psychotropic medication. The study was designed to examine prophylactic. i.e., recurrence-preventing (not relapse-preventing) properties of carbamazepine and lithium.[33] The recruitment process was carefully documented in order to investigate representativeness of selected patients. No substantial differences between study patients and nonstudy patients (i.e., patients who fulfilled all inclusion criteria but did not participate in the study) regarding sociodemographic and clinical characteristics such as sex, age at first occurrence of bipolar disorder, and number of previous episodes were found.[21] Hence, there is no evidence for a selection bias resulting from the recruitment process. Originally, the patients were selected according to ICD-9 criteria and diagnosed as suffering from manic-depressive or schizoaffective psychoses. This preselection of patients can be supposed to cover the whole spectrum of bipolar affective syndromes (with many of the ICD-9 schizoaffective patients being categorized as bipolar according to DSM-IV criteria). We therefore consider the results as essentially representative of bipolar patients hospitalized at a university center for an affective episode and in need of prophylactic treatment.

It has been argued that severe and atypical cases may be overrepresented in academic medical centers.[34] Major clinical variables such as number of previous episodes, severity of illness at beginning of study, presence of comorbidity, and mood-incongruent psychotic features[25,35] were, however, found to be unrelated to the risk of dropping out. Therefore, it seems unlikely that the results were strongly biased by inclusion of atypical patients. However, as our patients agreed to participate in a randomized, long-term trial, their willingness to maintain treatment and their trust in physicians and medications were probably above average compared with those of patients in ordinary clinical conditions. Similarly, we assume that the regular and intensive care associated with the study protocol diminished the dropout rate. In consequence, the variance in both the ICS and dropouts might have been reduced in the trial, and the impact of the patients' illness concepts and expectations with lithium treatment in an ordinary clinical setting might therefore be even stronger than in our study.

To test the influence of confounding clinical or sociodemographic variables, we compared the group of adherent and nonadherent patients for major clinical, sociodemographic, and psychological variables, and the possible confounders were included in multivariate analyses. To attain greater reliability when interpreting the results, we reanalyzed the major findings using a different statistical methodology. The impact of illness concepts on adherence to prophylactic lithium was consistently found in univariate (correlation and survival analyses) and multivariate (Cox regression, logistic regression) models.

With respect to dosage of study medications, our results can be extrapolated to clinical practice as the mean serum drug levels were within the currently accepted range for prophylactic treatment. Illness concepts might play an even greater role in treatment adherence of patients who need high serum drug levels, as these levels are usually related to more burdensome side effects.[36] The nonblind design of the study might, however, have introduced a bias as it cannot be excluded that because of the more recent introduction of carbamazepine as a mood stabilizer, the physicians were less confident in the efficacy and tolerability of carbamazepine as compared with lithium. In consequence, the physicians might (either consciously or unconsciously) have more readily motivated the patients to continue treatment when taking lithium (e.g., by informing the patient about the frequently reversible and harmless nature of some side effects such as nausea and polyuria). However, it is unlikely that in a double-blind study a study blind could be maintained over a treatment period of 2.5 years with 2 substances that present clearly different side effect profiles.[37,38] The potential bias due to the physicians' attitudes toward different medications is extremely difficult to eliminate in any long-term study of bipolar patients. As the same bias

reflects ordinary clinical practice, though, this methodological flaw would not seem to impede the generalizability of the results. For assessment of dropouts, the observation period of 2.5 years seems to be long enough as the rate of dropouts is generally highest during the early stages of long-term treatment.[15]

The major result from the present article concerning the lithium group is in accordance with the findings of the retrospective study by Schumann et al.,[15] who also report a clinically and statistically significant impact of illness concepts on adherence to prophylactic lithium. These results clearly encourage efforts to supplement pharmacotherapy with psychoeducation or psychotherapy[39,40] or to restrict prophylactic lithium treatment to sufficiently motivated patients. Our finding that with carbamazepine treatment higher scores of schizoidia were associated with shorter time to dropout was not hypothesis-driven and was accompanied by many negative findings regarding the impact of personality. The result should therefore be interpreted very carefully; to our knowledge, this study was the first to investigate the influence of premorbid personality on treatment adherence within a prospective design. Regarding predictive power of the sociodemographic and clinical variables investigated, higher age was the only variable that was significantly related to treatment adherence, a finding that is consistent with previous results.[41] However, other previous findings such as a positive relationship between female gender[2] or bipolar II (not I) disorder[17] and treatment adherence were not confirmed in our study.

In accordance with previous observations,[17,42] the number and severity of side effects were unrelated to treatment adherence in our study. In contrast to these results, Gitlin et al.[43] found lithium discontinuation to be related to coordination and cognition side effects, and Maarbjerg et al.[44] found somatic side effects to be a frequent reason for stopping medication. Our results indicate that treatment adherence is unrelated to the actual number and severity of adverse events but negatively influenced by the *subjective* impairment due to side effects (data not shown). At present, the role of sociodemographic and clinical predictors remains inconclusive. A recent analysis of our data showed a positive relation between high interepisodic morbidity and nonadherence to prophylactic treatment.[24]

In conclusion, patients' illness concepts—especially trust in medication and in the treating physician—had a clear impact on adherence to prophylactic lithium treatment. As this relation was found to be independent of major covariates such as age, sex, and important clinical and psychological variables, illness concepts seem to be a very promising working point for psychoeducation and psychotherapy. This is in line with findings of a positive effect of an education program on lithium compliance.[14] These results might also be of relevance for prophylactic treatment with other mood stabilizers associated with disturbing side effects such as weight gain.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others).

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Appendix 1. Dimensions of the Illness Concept Scale[a]

TM (trust in medication) = items 2, 7, 16, 19, 25
TP (trust in the treating physician) = items 3, 6, 17, 20
NE (negative treatment expectations) = items 10, 14, 18, 21, 28
GT (guilt) = items 15, 22, 24
CC (chance control) = items 4, 8, 11, 13, 27
SC (susceptibility) = items 1, 9, 26
IA (idiosyncratic assumptions) = items 5, 12, 23, 29

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Appendix 2 appears on page 974.

Appendix 2. Illness Concept Scale[a]

Here you find some statements on health and medical treatment, reflecting opinions of patients. Please mark whatever you think is most appropriate.

I agree with the following statement:	Not at all	A little bit	Somewhat	Mostly	Yes, very strongly
1. If I get sick, it is usually serious					
2. Medication is keeping my health stable					
3. If I consult a doctor, I know I will receive help					
4. Being healthy is mainly a matter of good luck					
5. Taking medications means that I cannot solve my problem myself					
6. If I am sick, good medical care is the best way for me to recover					
7. With psychiatric illnesses, people have to trust drug treatment					
8. Whether I get well or not is a matter of chance					
9. I have to be on guard not to get sick					
10. Taking medications hinders my daily activities					
11. There are so many illnesses that it is almost a miracle to be healthy					
12. Psychological suffering cannot be cured by medical drugs					
13. If there is an illness in my body, I will get sick no matter what I do					
14. I am afraid that medication can alter my personality					
15. If I get sick, it is mainly because I have neglected to take care of myself					
16. I always respond well to medication					
17. The best thing to do is to follow the advice of the doctor					
18. I am afraid that other people will look down on me if I take medication					
19. Medication is of great help in psychiatric disorders					
20. The best way to stay healthy is to consult a doctor regularly					
21. People lose their grip on reality when they take medications					
22. When I get sick, it is usually because I have done something wrong					
23. All medications have to be stopped at some point in time					
24. When I get sick, I know that I have not done enough exercise or eaten a healthy diet					
25. If I take the right medication it will help me					
26. I have to look after my health very carefully					
27. People who do not get sick are just lucky					
28. To take medication is simply a burden					
29. Natural healing is always better than drug treatment					

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