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Comparison of the Clinical Efficacy of Carbamazepine and Haloperidol as Adjuncts to Lithium in Patients in an Acute Manic Phase: A Double-blind Clinical Trial

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Abstract

There is abundant evidence that the efficacy of the carbamazepine-lithium combination in acute manic episodes is comparable to that of other custom medications (e.g., a haloperidol-lithium combination). The aim of the current investigation was to compare the clinical efficacy and side effects of lithium combined with carbamazepine versus lithium combined with haloperidol and biperiden in patients with bipolar disorder. In the present study, 24 patients in an acute manic phase were randomly assigned to receive either lithium-carbamazepine (Li-CBZ) or lithium-haloperidol (Li-Hal) combinations for 8 weeks. Clinical (including ESRS, MRS, CBZ side effect profile, and HAM-D) and laboratory measurements were regularly performed on all patients. Both therapeutic regimens were effective in alleviating manic symptoms, whether psychotic features were present or not ($p<.001$). However, there was a faster response to treatment for the Li-CBZ group compared to the Li-Hal group, as revealed by a lower mean MRS score on day 14 in the former group ($p=.018$). HAM-D scores revealed significantly better outcomes for the Li-CBZ group. A higher mean HAM-D score on day 56, as well as a higher mean alteration in HAM-D scores throughout the study period, were noted in the Li-Hal group ($p=.008$ and $p=.011$, respectively). Dropouts in the Li-Hal group were considerable due to noncompliance resulting from neuroleptic-induced side effects (depressive and extrapyramidal). Similarly, several subjects in the Li-CBZ group had to end the study prematurely as a result of developing side effects for which drug discontinuation is indicated. It may be prudent to reevaluate neuroleptic medications in manic patients, specifically for long-term management.

Keywords: Mania; Lithium; Carbamazepine; Extrapyramidal.

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Introduction

Lithium has been the main therapeutic treatment for patients suffering from mania

since its introduction as an antimanic agent in 1949 (Cade, 1949). Many patients, however, remain unresponsive to lithium alone, or are unable to tolerate its side effects. Clinically, it is common practice to combine lithium with other drugs, especially antipsychotics, in order to rapidly sedate patients and to improve psychotic symptoms. This is in view of the results of a study by Prien, Caggery, and Klett (1972), which demonstrated the greater efficacy of chlorpromazine as compared to lithium in hyperexcitable manic patients.

Post, Ketter, and Callahan (1994) pointed out the development of extrapyramidal side effects and dysphoric mood in manic patients for whom neuroleptics were used as an adjunctive treatment. Additionally, there were increased incidences of tardive dyskinesia and protracted depressive disorders if the combination had been continued as a prophylactic treatment. It has been proposed that the major cause of relapse in affective patients was noncompliance with medications, which was predominantly due to the development of lithium side effects (Silverstone & Romans, 1996). Nowadays, it is widely accepted that there are similarities between pathophysiological processes of affective disorders and some movement disorders (Cummings, 1992; Mayberg, 1997; Nillson, Kessing, & Bolwig, 2001; Shiba, Bower, & Maraganore, 2000). Patients suffering from affective disorders are prone to developing extrapyramidal side effects in response to neuroleptic drugs, including tardive dyskinesia (Yassa, Ghadirian, & Schwartz, 1983), neuroleptic-induced dystonia (Nasrallah, Churchil, & Hamdan-Allan, 1988), and neuroleptic malignant syndrome (Susman & Addonizio, 1988). Carbamazepine, an anticonvulsant drug possessing mood-stabilizing and antimanic effects, can also be combined with lithium in the treatment of acute mania (Dardennes, Even, Bange, & Heim, 1995; Denicoff et al., 1997; Elphick, 1989; Keck, Mcelroy, & Strakowski, 1998; Licht, 1998).

Although it is widely recommended that acute manic episodes be treated with a combination of therapeutic drugs, there are few randomized studies that compare the efficacy and side-effect profiles of well-established drug combinations (Keck et al., 2000). Small et al. (1995) have reported an advantage of fewer incidences of the aforementioned neuroleptic side effects in treatments of lithium combined with carbamazepine versus haloperidol. However, some authors have found the lithium-carbamazepine combination to be more liable to produce neurotoxic effects. In the

present study, we undertook a double-blind, randomized clinical trial with relatively rigid inclusion and exclusion criteria to compare the efficacy and side-effect profiles of lithium (Li) combined with either carbamazepine (CBZ) or Haloperidol (Hal) in the treatment of patients hospitalized for an episode of acute mania.

Materials and Methods

Participants

The study was undertaken in a teaching psychiatric hospital in Iran during an 18-month period. Patients were referred to this center often after insufficient or ineffective ambulatory treatment by out-patient psychiatric facilities or by private psychiatrists.

Inclusion criteria stressed that patients should be 18 to 65 years of age, have at least one well-defined manic episode in their past psychiatric history, and fulfill DSM-IV criteria for the diagnosis of "bipolar mood disorder, most recent episode manic" (either with or without psychotic features) (American Psychiatric Association, 1994), which was established by the attending psychiatrists. Patients were also required to meet none of the exclusion criteria. The exclusions were any other concurrent Axis I diagnosis, including cyclothymic disorder, rapid-cycling mood disorders, and mood disorders due to a general medical condition or substance abuse. Additionally, patients who fulfilled DSM-IV diagnostic criteria for any Axis II diagnosis were excluded. Patients with any contraindication to the use of study medications, namely lithium, carbamazepine, haloperidol and biperiden, as well as those with any major medical or neurological problems interfering with psychopathological processes or therapeutic procedures (e.g., pregnancy, breast feeding, consumption of other drugs, known to have interactions with study medications, etc.) were also excluded from this study.

Written informed consent was obtained from patients who fulfilled all of the inclusion criteria and met none of the exclusions. Twenty-four patients entered this study and were randomly divided into two groups (Li-Hal and Li-CBZ groups). This randomization was achieved through the hospital's pharmacy, which had no direct contact with admitted patients and which was blind to the results of clinical and laboratory evaluations.

Drugs

After a one-week period of drug washout, during which the initial investigations were performed, patients received lithium either with haloperidol and biperiden, or with carbamazepine, according to their medication group. The adjunctive medication, either carbamazepine (CBZ) or haloperidol (Hal) and biperiden, were reformulated by the hospital's pharmacy into identical purple-red capsules to maintain the blindness of ward staff and patients. Each capsule in the Li-Hal group contained 5 mg of haloperidol and 2 mg of biperiden, and in the Li-CBZ group, 200 mg of carbamazepine.

The initial medication dose was 300 mg of lithium (Li) plus one study capsule twice daily; this dose was increased every three to four days until desirable plasma levels of drugs were achieved. The desirable plasma level was between 0.8 and 1.2 mmol/L for lithium and 6 to 12 μg/mL for CBZ.

Dosages of each medication were titrated for achieving symptomatic relief, maintaining desirable plasma levels, or for the development of serious side effects. A final-year psychiatry postgraduate student performed the titration of medications. Due to the nature of the generic drug program in Iran, total amounts of medications required for the study were estimated and obtained from a single manufacturer at the beginning of the study.

During the first week of the drug-free period and throughout the eight weeks of treatment, only rescue medication (namely, injectable diazepam for agitated or dangerous behavior, and oral flurazepam as a hypnotic drug at nighttime) were permitted, if needed, but not within 12 hours of evaluations.

Assessments

Assessment upon admission included a careful examination of patients' psychiatric and medical history, a thorough physical examination, complete blood counts (CBCs), thyroid function tests (TFTs), hepatic enzyme evaluations, renal function tests (including blood urea nitrogen, serum creatinine, and serum sodium and potassium levels), fasting blood sugar, triglyceride and cholesterol levels, and ECG measurements. All laboratory assessments were repeated on days 28 and 56 after the initialization of medication treatment, except for TFTs and ECG, which were done only at baseline and on day 56. Participants' serum lithium levels were initially

assessed one week after commencement of medication treatments and then on a weekly basis throughout the eight-week period of the study. Serum carbamazepine levels were evaluated one and two weeks after commencement of medication treatments, and then biweekly in Li-CBZ patients as well as in the Li-Hal group to maintain patients' and raters' blindness.

Another senior resident of psychiatry, who was blind to the study groups, performed psychiatric assessments and evaluations of the extrapyramidal and other neurological and medical complications of the study medications. Assessments included the Mania Rating Scale (MRS; Young, Biggs, Ziegler, & Meyer, 1978), the Extrapyramidal Symptom Rating Scale (ESRS; Simpson & Angus, 1970), and the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960), which were completed initially at baseline, then weekly for two weeks, and biweekly thereafter. Additionally, common complications of carbamazepine, namely dizziness, ataxia, clumsiness, sedation, dysarthria, diplopia, nausea, vomiting, diarrhea, constipation, anorexia, tremor, memory disturbances, confusion, orthostatic hypotension, and weight gain, were also assessed and scored 0 if not present, 1 if mild, 2 if moderate, and 3 if severe.

The development of carbamazepine complications for which drug discontinuation is indicated was also assessed; patients who developed any of these complications were not retained in the study. These included signs of bone marrow problems (fever, sore throat, petechiae and easy bruisability), signs of liver problems (jaundice, right upper quadrant abdominal pain, and increases in liver enzymes above 3 times the upper normal limit [UNL]), and signs of skin problems (erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, or any other rashes).

Patients with MRS scores below 7 at any time during the eight-week period of medication treatment were discharged from the ward and followed up through an outpatient setting. Follow-ups of psychiatric evaluations, and laboratory evaluations and medication titration, were conducted separately by two residents to ensure blindness of the raters. Separate forms for each day of visit, which included all assessments required for that day of the study, were designed to prevent previous ratings from having any impact on current evaluations.

Analysis

All of the evaluations and analyses were performed by repeated-measures ANOVA, *t*-tests, and Mann-Whitney tests using SPSS.

Results

Demographic data and indicators of severity of illness, including the MRS score on admission and positive items according to seven sub-criteria of the DSM-IV criterion B for acute manic episodes, have been summarized in Table 1. The mean age was 33.41 for the Li-Hal group (*SD*=7.41) and 34.08 for the Li-CBZ group (*SD*=7.05). There was no statistically-reliable difference between the two groups in terms of demographic data. The mean difference of MRS scores on admission was -4.3, with a 2-tailed significance of .269, which was not statistically significant. Additionally, the number of positive items according to seven sub-criteria of the DSM-IV criterion B for acute manic episodes revealed no reliable group differences (Mann-Whitney test).

Among 12 patients in the Li-Hal group, eight patients completed the 56-day period of the study. One patient failed to complete the study due to noncompliance as a result of lack of insight (Table 1); three patients withdrew from medication treatments due to the emergence of such complications as dysphoric mood, feeling of inner tension, or lack of energy. Nine of 12 patients in the Li-CBZ group remained in the study for the entire period; one patient was omitted from the study because the medications were ineffective despite sufficient dosing, and two were dropped as a result of developing CBZ complications for which drug discontinuation is indicated (one due to the appearance of a skin rash, and one due to elevation of liver enzymes above 3 times UNL). The difference in the number of patients completing the full study period was not significant between the two groups (p=.65).

Repeated-measures ANOVA of MRS scores revealed significant improvements over time for both groups (p<.001); the process of improvement as a whole did not differ significantly between the two groups (p=.496). However, mean MRS scores on day 14 were 21.3 for Li-Hal patients (*SD*=4.03) and 16.7 for Li-CBZ patients (*SD*=4.86). Li-CBZ patients showed a significantly better MRS score on day 14 (p=.018, t=2.558, df=22, F=.604, 95% CI of difference: .88 - 8.45). Comparisons of relevant data on days 0, 3, 7, 28, 42, and 56 revealed p-values that were not statistically significant (.269, .680, .855, .826, .156, and .052, respectively). A diagram of

improvement in MRS scores in both groups is presented in Figure 1. Comparisons for each MRS item between the two groups led to similar results. In contrast, the mean duration of the period for each group over which MRS scores decreased by 50% was not associated with the type of therapeutic regimen (p=.734).

Table 2 shows the mean total scores on the Hamilton Rating Scale for Depression (HAM-D) on days 28 and 56, as well as the mean alteration in HAM-D scores throughout the 56 days of evaluation. Mean total HAM-D scores on day 56 were significantly higher in the Li-Hal group than in the Li-CBZ group (p=.008, 95% CI of difference: 1.86 - 9.93). Additionally, there was a significant difference between the two groups in terms of total HAM-D score alterations over the study period, which were 1.4 and -3.8 for the Li-Hal and Li-CBZ patients, respectively (p=.011, 95% CI of difference: 1.34 - 9.06).

Mean total ESRS scores on days 28 and 56 and mean total ESRS score alterations over the second half of the evaluation period (from days 28 to 56) are also summarized in Table 2. In spite of noticeable differences in mean ESRS scores on day 28 (11.58 for the Li-Hal group and 4.91 for the Li-CBZ group), no significant difference was noted between the two groups. The prevalence of the aforementioned common CBZ complications was not significantly greater in Li-CBZ patients than in Li-Hal patients. Repeated-measures ANOVA for each laboratory evaluation over time revealed no statistically-reliable group differences. Covariant analyses of ESRS results on days 28 and 56 and ESRS score alterations from days 28 to 56, with an adjustment for HAM-D results, also did not reveal any statistically-reliable group differences (p=.163, p=.567, and p=.228, respectively).

Figure 2 shows the alterations in serum lithium levels over time according to therapeutic group, which were associated with time in both groups. Additionally, serum lithium levels in each group were inversely associated with MRS scores (p<.001). This finding was not found for serum CBZ levels.

Mean admission duration was 34.25 days for Li-Hal patients (SD=4.90) and 32.58 days for Li-CBZ patients (SD=10.28). The difference between the two groups on this measure was not significant (p=.619). As mentioned previously, reasons for study termination were recorded and subdivided into six categories, the results of which are summarized in Table 1. Differences between the two groups were not

statistically significant.

Discussion

Lithium is an effective medication in acute and maintenance treatment of mania; however, approximately 50% of manic patients exhibit inadequate responses to lithium or suffer from intolerable side effects (Post et al., 1996). Reportedly, many psychiatrists prefer prescribing a combination of lithium and antipsychotic medications in the treatment of mania (Oshima et al., 1999; Sernyak & Woods, 1997; Tohen et al., 2001). There are accumulating well-designed research data on the efficacy of carbamazepine in alleviating the symptoms of manic episodes with comparable efficacy to lithium. The clinical importance of the existence or nonexistence of psychotic features in mania is a matter of debate. Some experts dispute the *continuum psychosis hypothesis* and point out the inherent differences of manic psychoses in comparison to non-affective psychoses (Coryell et al., 2001). Several authors have proposed that carbamazepine may exert antipsychotic activity at least in the early stages of treatment when a carbamazepine-lithium combination was used to treat manic symptoms (e.g., Okuma, 1993). Thus, from a clinical standpoint, it appears to be prudent to prefer a lithium-haloperidol combination as a sedative medication when a patient is very aggressive (Cookson, 2001). However, when aggressiveness is not present, the development of psychotic features in manic patients does not by itself necessitate initiation of antipsychotic medications, as was reported by Coryell et al. (2001), who compared the clinical efficacy of lithium alone in patients with psychotic versus nonpsychotic affective disorders. Their comparison of efficacies revealed no clinically reliable differences.

The present double-blind randomized study of lithium combined with carbamazepine or with haloperidol in the treatment of mania demonstrates the prominent efficacy of both combinations in treating the disorder, regardless of the presence of psychotic symptoms. The major difference between the two therapeutic regimens lay in the type and severity of side effects. Medication ineffectiveness was noted more among the carbamazepine-lithium group with high aggressiveness. Additionally, patients receiving the carbamazepine-lithium combination experienced more complications of carbamazepine for which drug discontinuation is indicated. Alternatively, patients receiving the haloperidol-lithium treatment had

a higher proportion of dropouts for noncompliance as a result of extrapyramidal and depressive complications, as evidenced by higher HAM-D scores on days 28 and 56 and more substantial alterations in HAM-D scores over the course of the study period. Furthermore, there were considerably higher mean scores on extrapyramidal symptom ratings, especially on day 28. However, this difference was not statistically significant in the carbamazepine-lithium group due to substantial within-group heterogeneity and to small sample sizes. As reported by several authors (e.g., Small et al., 1995), evidence is accumulating for a more rapid response to treatment when administering a carbamazepine-lithium combination as opposed to a haloperidol-lithium combination, a finding that is confirmed by the significantly lower mean MRS scores on day 14 in the Li-CBZ group. Non-significance of differences of MRS results between the two groups according to point-to-point comparisons cannot be assumed to be type 1 errors because the *p*-values were far beyond significance.

Small sample sizes were our major limiting factor. Additionally, it might be preferable to evaluate psychotic symptoms and improvement in its clinical manifestations by means of other specific measures, such as BPRS and GAF scores.

Although the present study replicates some of the results obtained by Small et al. (1995), other double-blind studies with a larger number of patients should be conducted to confirm the results of the present study.

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Table 1. Comparison of demographic data and severity and outcome indicators in the two groups

Variable	Li-Hal Group	Li-CBZ Group
Mean Age (*SD*)	33.41 (7.41)	34.08 (7.05)
Sex		

Male	8	5
Female	4	7
Marital Status		
Single	3	4
Married	6	7
Divorced	2	1
Widowed	1	0
Number of previous episodes		
1-2	5	7
3-4	5	3
>4	2	2
Positive items among 7 subcriteria of DSM-IV Criterion B		
4	2	5
5	4	4
6	6	2
7	0	1
Baseline Mean MRS Score (*SD*)	26.7 (5.54)	33.2 (12.33)
Reasons for Study Termination		
Termination at end of 8-week period	8	9
Lack of drug efficacy	0	1
Noncompliance as a result of lack of insight	1	0
Noncompliance as a result of side effects (e.g., lack of energy, sense of inner tension, daytime sleepiness, etc.)	3	0

Development of side effects for which drug discontinuation is indicated	0	2
Relapse	0	0

Table 2. Comparison of Hamilton Rating for Depression (HAM-D) total scores and ESRS total scores on given days of evaluation

Variable	Li-Hal Group	Li-CBZ Group	*p* Value
Mean total Hamilton score on day 28 (*SD*)	3.5 (14.7)	.8 (1.8)	.084[a]
Mean total Hamilton score on day 56 (*SD*)	7.2 (5.3)	1.3 (2.4)	.008[b]
Mean alteration in Hamilton scores from day 0 to day 56 (*SD*)	1.4 (5.1)	-3.8 (2.6)	.011[c]
Mean total ESRS score on day 28 (*SD*)	11.58 (11.57)	4.91(5.31)	.089[d]
Mean ESRS score on day 56 (*SD*)	2.3 (2.94)	1.9 (2.07)	.73[e]
Mean alteration in ESRS scores from day 28 to day 56 (*SD*)	8.4 (12.93)	2.4 (3.34)	.185[f]

[a] t=1.86, df=22, F=16.123

[b] t=3.170, df=18, F=14.960

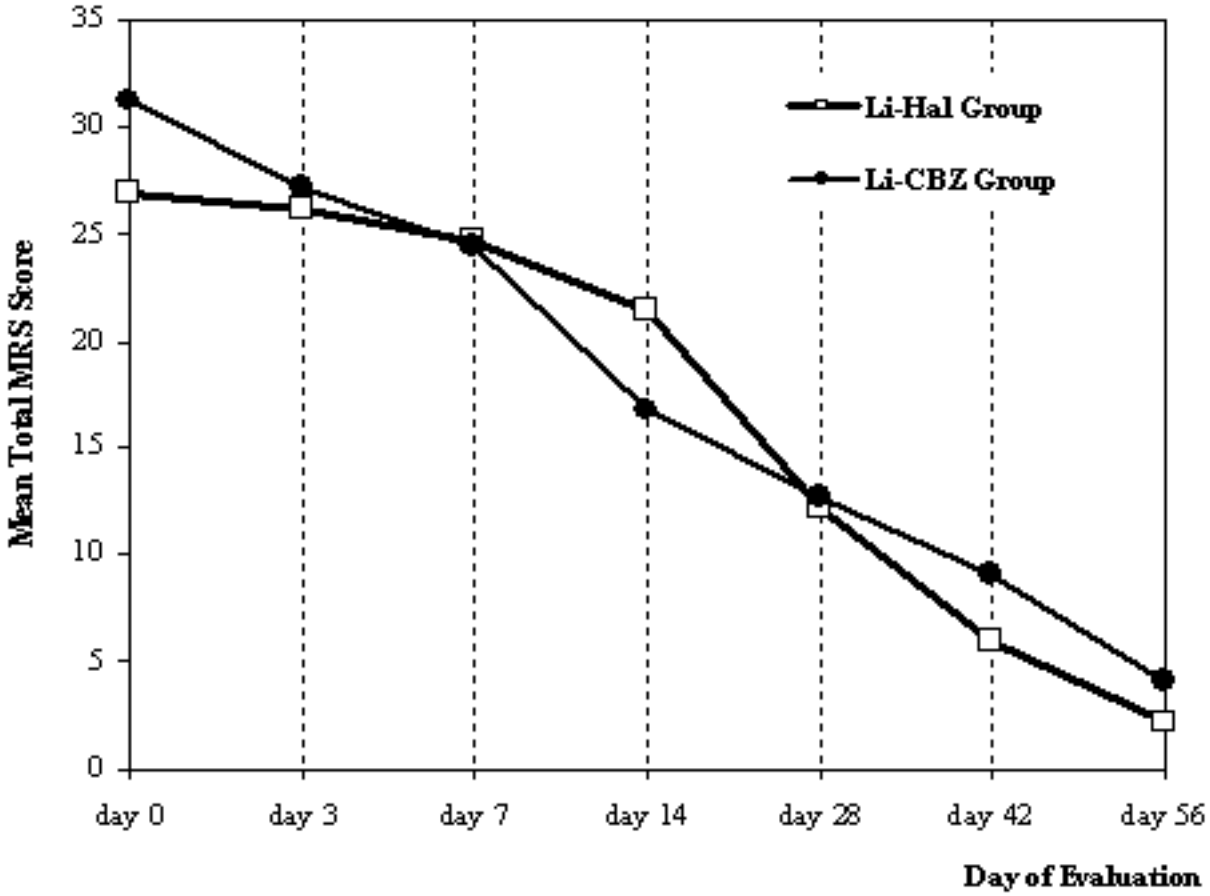
[c] t=2.829, df=18, F=7.615

[d] t=1.814, df=15.446, F=5.378

[e] t=.351, df=16.183, F=2.582

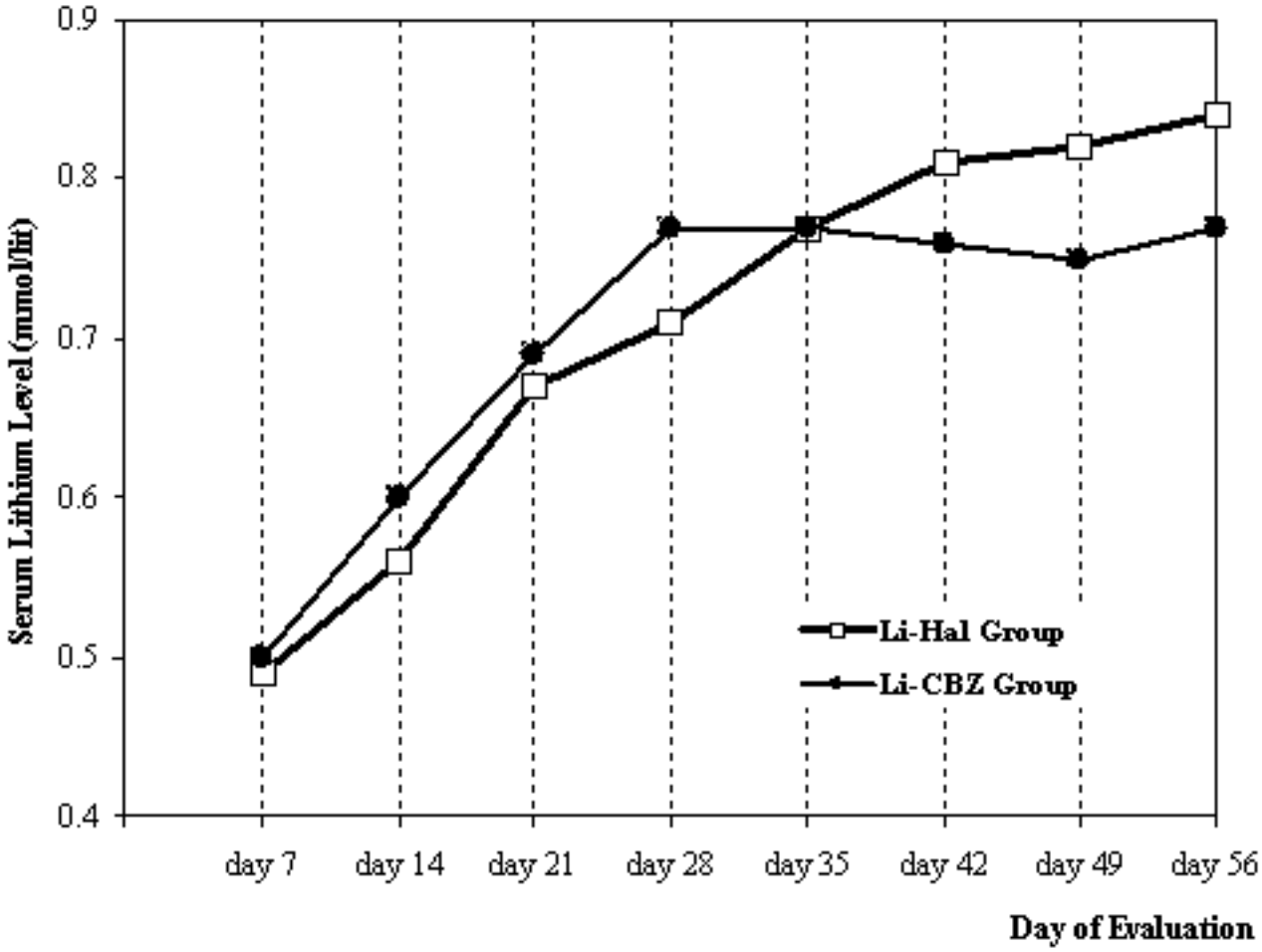
[f] t=1.420, df=10.194, F=9.498

Figure 1. Mean total MRS score alterations according to patients' therapeutic group.



	day 0	day 3	day 7	day 14	day 28	day 42	day 56
Li-Hal	26.83	26.17	24.67	21.33	12.17	5.92	2.2
Li-CBZ	31.17	27.17	24.33	16.67	12.67	9.09	4.1
p-value	.269	.680	.855	.018*	.826	.156	.052
t	-1.133	-.417	.184	2.558	-.223	-1.473	-2.117
F	1.947	.000	2.216	.604	.878	11.251	.293

Figure 2. Serum lithium level alterations according to patients' therapeutic group.



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