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The comparative efficacy of carbamazepine low and high serum level and lithium carbonate in the prophylaxis of affective disorders

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Summary

The prophylactic efficacy of carbamazepine slow release (CBZ) at ke different blood levels and lithium carbonate slow release (LI) was compared in a retrospective/prospective, randomized, 2-year open trial. 84 patients with a DSM-III-R diagnosis of recurrent affective disorder who had no prophylactic medication in the 2 years preceding the trial (no LI nonresponders), were randomly allocated to three treatment groups: CBZ low (15–25 $\mu\text{mol/l}$), CBZ high (28–40 $\mu\text{mol/l}$) and LI (0.6–0.8 $\mu\text{mol/l}$). Fifty-eight patients completed the full observation period of 2 years, 26 patients dropped out. There were no statistically significant differences in the efficacy of the prophylactic treatment for bipolar patients. For the unipolar patients, the group with a low CBZ serum level showed no reduction in the duration of episodes. The two other treatment groups seem to be equal in attenuation of a unipolar course of an affective disorder.

Key words: Carbamazepine; Lithium; Affective disorder; Prophylactic efficacy

Introduction

There is increasing evidence that carbamazepine may be the most promising alternative substance to lithium in preventing recurrences of

affective psychoses. Carbamazepine, a carbamylidibenzoazepine derivate, was developed in 1957 as an anticonvulsant drug and has structural similarities to tricyclic antidepressants like imipramine. From the earliest Japanese reports in the 70s (Takezaki and Hanaoka, 1971; Okuma et al., 1973), case reports and uncontrolled open clinical trials support the evidence that the antimanic and prophylactic efficacy of carbamazepine in manic-depressive illness is comparable to the effective-

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ness of lithium salts (detailed reviews: Schmidt and Greil, 1987; Demisch et al., 1989; Prien and Gelenberg, 1989; Finzen, 1991).

However, the present literature leads to the conclusion, that carbamazepine seems to be an alternative drug for prophylactic treatment of manic-depressive illness especially in patients who fail to respond to lithium as well as patients with a rapid cycling course (Kishimoto et al., 1983, Stuppaeck et al., 1990).

Up to this moment there is only one randomized and controlled prospective trial to evaluate over a longer period and a larger sample the capacity of carbamazepine in the prophylactic treatment of recurrent affective psychoses (Placidi, 1986).

Until now there are only a few studies, which compare the efficacy of carbamazepine against placebo. One study was published by Okuma et al. in 1981. This study covered an observation period of 1 year with 10 patients allocated to carbamazepine medication and was compared to 9 patients on placebo. The difference between the two groups was not statistically significant, but carbamazepine appeared to be more effective than placebo in prophylactic treatment.

Ballenger and Post (1980), Post et al. (1983), and Post and Uhde (1985) reported the efficacy of carbamazepine using an 'on-off design' against placebo. They showed the positive acute efficacy in manic and depressive episodes, as well as the usefulness of carbamazepine in maintenance treatment, especially in patients with a rapid cycling course.

Over the years, several studies compared the efficacy of carbamazepine with lithium salts. Placidi et al. (1986) investigated in a randomized, double-blind 3-year trial, the acute and prophylactic efficacy of carbamazepine versus lithium in 83 patients with major affective, schizoaffective and schizophreniform psychosis. In the patients with affective disorder there is no statistically significant difference in rates of improvement or deterioration between the two treatment groups. Lithium and carbamazepine appear equipotent in preventing relapses in two thirds of the patients and both seem to prevent more the excited rather than the depressive symptoms.

Watkins et al. (1987) compared in a random-

ized double-blind retrospective/prospective trial, the mood stabilizing efficacy of carbamazepine and lithium in maintaining the remission following an acute episode. Over a period of 1 year, 37 bipolar or unipolar patients were observed and lithium was found significantly more effective in prolonging the time of remission. 23 out of 38 patients had guessed their medication correctly, in spite of double-blind conditions because of prior experience with lithium carbonate.

Lusznat et al. (1988) compared the efficacy of lithium carbonate versus carbamazepine in a double-blind 1-year follow-up study on 54 admitted patients because of acute mania. In 95% of the cases the manic episodes were part of a bipolar course of affective disorder. With the remaining 33 patients, carbamazepine was found to be slightly more effective than lithium in preventing relapses. Patients on carbamazepine experienced significantly fewer mood swings and relapses into mania or depression were delayed.

Demisch (1991) found in his study with 89 patients from 14 different investigation centres over 2 years, a mild superiority in the prophylactic efficacy of carbamazepine in unipolar affective and schizoaffective patients. In bipolar patients there was a mild tendency of superiority towards lithium. There were no statistically significant differences between lithium and carbamazepine treatment regarding efficacy and safety.

Coxhead (1992) treated 40 bipolar patients, who were stable on lithium, in a randomized double-blind design with lithium or carbamazepine over 12 months. The authors found that carbamazepine is equal regarding efficacy and tolerability to lithium in the prophylaxis of bipolar disorder in patients not selected for their nonresponsiveness to lithium.

The results of these trials clearly indicate that carbamazepine is a promising alternative to lithium in long-term treatment of recurrent affective psychoses but there is only one study which reached a longer observation period of more than 1 year. Several patients were so called lithium nonresponders and numerous studies refer to patients with rapid cycling. All trials so far conducted generally indicate that carbamazepine is equal in relapse prevention to lithium. Nevertheless lithium is recommended as the drug of first

choice and there is no clear recommendation concerning the optimal 12-h carbamazepine serum level for relapse prevention. The above-mentioned studies show a similar side effect index of both drugs.

The aim of our study was to compare the efficacy in relapse prevention of lithium carbonate and carbamazepine over a period of 2 years with patients who fulfilled the criteria for a prophylactic treatment (Angst, 1981) and had received no prophylactic medication of more than 3 months within the last 2 years before commencing the trial. In contrast to other investigations (Stuppaeck et al., 1990) we wanted to exclude lithium nonresponders.

By using two groups with different average carbamazepine serum levels, we chose an open design and tried to get closer to the question how high the 12-h carbamazepine serum level should be for successful prophylactic treatment.

Patients and methods

181 in- and outpatients referred for prophylactic treatment of recurrent affective disorder to the outpatient clinic of the Psychiatric Department of the University of Vienna and were screened consecutively between April 1987 and December 1988 for entering the trial.

All patients who fulfilled the inclusion criteria, male and female, between 18 and 75 years with unipolar or bipolar recurrent affective disorder according to DSM-III-R (296.), and with at least one episode within the last 2 years before the index episode were considered.

Patients who suffered from alcoholism, drug abuse, severe renal, cardiovascular, pulmonary, hematologic, liver or neurological diseases were excluded from the trial. No DSM-III-R diagnosis of the schizophrenic group (295.) was allowed. It should also be noted that patients who had received prophylactic medication for more than 3 months within the last 2 years were excluded.

84 patients, who gave their informed consent, and whose relatives were informed too, were randomly assigned to three treatment groups in an open prospective 2 year trial. At the time of randomisation the patients had moderate symptoms at the end of the index episode:

(1) a carbamazepine slow-release * group with a 12-h serum level between 15 to 25 $\mu\text{mol/l}$ (CBZ-LOW); or

(2) a carbamazepine slow-release * group with a 12-h serum level between 28 to 40 $\mu\text{mol/l}$ (CBZ-HIGH); and

(3) a lithium carbonate slow-release ** group * with a 12-h serum level within the range of 0.6 to 0.8 mmol/l (LI). Serum levels were adjusted within the first 8 weeks.

A placebo control group (over 2 years) was not used for ethical reasons.

The carbamazepine serum levels were measured by Syva (Merck emit technique) and the lithium serum levels with an ion selective electrode.

Age, sex, duration of illness, onset of the illness, number of hospitalisations, duration of episodes (depressive and manic) and symptom-free intervals were recorded especially for comparing retrospectively the 2-year period before the index episode and prospectively the 2 years under prophylactic treatment. After the first and second years, two trained psychiatrists together with the patient and the relevant data, gave clinical judgement whether or not there was a modification in the course of the disease. For clinical judgement the following aspects were taken into consideration: duration and intensity of episodes, duration of hospitalisations, additional medication, social integration with the family and work. In order to complete this rating we could contact personally 80.7% of the dropped out patients.

For clinical evaluation Clinical Global Impression (CGI), Brief Psychiatric Rating Scale (BPRS) and Bech-Raffaelson melancholia/mania rating scale were used. At the beginning of the trial, during week 2, 4, 6, 8 and later bimonthly, the following laboratory analyses were done in all cases fasting between 7.30 to 8.30 a.m.: 12-h serum level (lithium or carbamazepine), complete blood cell count, electrolytes, serum glutamic oxalacetic (SGOT), serum glutamic pyruvic transaminase (SGPT), gamma glutamyltransferase, alkaline phosphatase, serum proteins, creatinine,

* Neurotop Retard 300 mg (Gerot Pharmazeutica)

** Quilonorm Retard 450 mg (Smith Kline Beecham)

blood urea nitrogen. At baseline, after the first and second year of observation thyroid hormones, EEG and ECG were done.

All compounds used in the trial were slow release preparations and the dosage of test drugs was increased slowly within 8 weeks until the serum level of the randomized group was reached. At every clinical visit each patient was requested to complete a side effect list and this was later discussed with the doctor conducting the rating.

The study was not terminated even when a relapse, either manic or depressive, occurred during the test period. Patients were advised to come to additional visits if they experienced mood changes lasting longer than 3 days. They had to continue prophylactic medication and were given rescue medication as required by the clinical picture for as short time as possible. It was necessary to observe and measure the duration of episodes during prophylactic treatment under naturalistic conditions (Watkins, 1987).

Efficacy was measured by comparing the weeks in which a patient was in a manic or in a depres-

sive episode, the time in free interval and the number of hospitalisations 2 years before starting prophylactic treatment with the weeks of illness during the observation period excluding the index episode. Moreover, an overall clinical judgement was done by two trained psychiatrists together with the patient after analysing all available data.

Data were collected on a data base developed by the authors (Simhandl et al., 1989). Statistical analyses were performed with the SPSS-PC + package using frequencies, crosstabs, chi-square, *t*-test, Kruskal-Wallis test (generalised *U*-test) for comparison between the three groups, and the Wilcoxon matched pairs signed rank test for comparing within groups before and during 2 years, as suggested by Prien (1989). For the survival curve the Kaplan-Meier method was used to produce the graph. Other statistical tests were not allowed because of inhomogeneity of variances and no normal distribution in groups. As level of significance we chose an alpha at the 5% level and a beta error of 20%, calculated for 50% reduction of the mean duration of depressive

TABLE 1

Treatment group	Patient description							
	Total	CBZ-LOW		CBZ-HIGH		Lithium		
No. of patients	84	30		28		26		
Age mean *	42	42		45		42		
stdev	13	12.6		13.8		12.6		
* Anova: age <i>F</i> 0.621; <i>P</i> = 0.541.								
Beginn of illness	1978	1978		1977		1980		
Duration (month) mean **	111	123		128		89		
stdev	96.0	78.4		114.2		93.6		
** Anova duration: <i>F</i> 0.976; <i>P</i> = 0.383.								
Male	26	31.0%	6	7.1%	7	8.3%	13	15.5%
Female	58	69.0%	24	28.6%	21	25.0%	13	15.5%
Chi-square: 6.56180, df: 2, <i>P</i> = 0.0376.								
Unipolar	32	38.1%	13	15.5%	14	16.7%	5	6.0%
Bipolar	52	61.9%	17	20.2%	14	16.7%	21	25.0%
Chi-square: 5.95518, df: 2, <i>P</i> = 0.5909.								
Finished	58	69%	19	22.6%	18	21.4%	21	25.0%
Dropped out	26	31%	11	13.1%	10	11.9%	5	6.0%
Chi-square: 2.42693, df: 2, <i>P</i> = 0.2972.								

episodes before and after a 2-year treatment (Cohen, 1969). Biometric advisory was done by Prof. Dr. K. Kubinger from the Department of Psychology, University of Vienna.

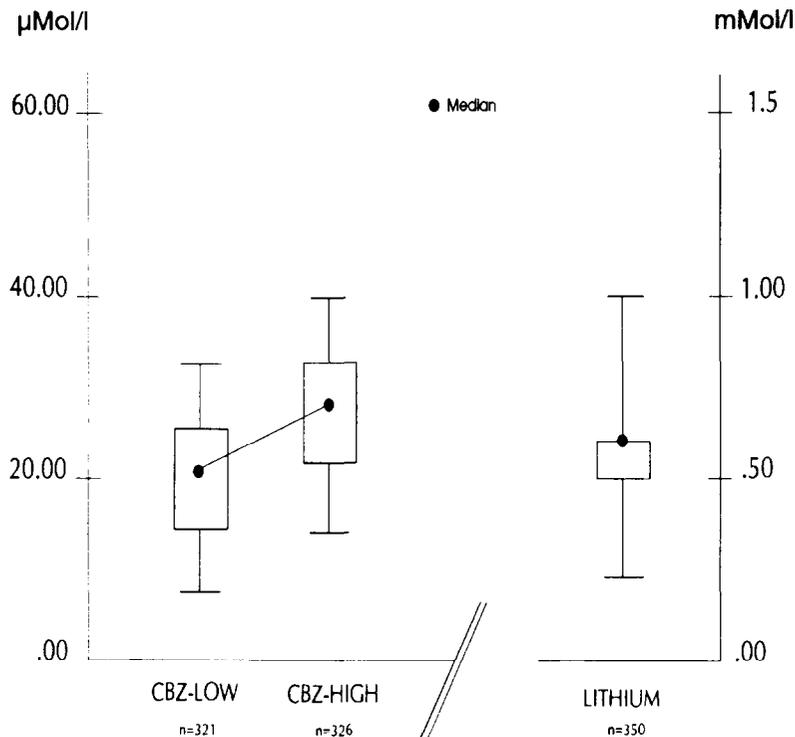
Results

The patients in the three treatment groups were comparable regarding age, age of onset, onset of disease, and duration of illness (*t*-test NS, see Table 1). There were 6 patients with psychotic features in the unipolar group ($n = 32$) and 19 patients with psychotic features in the bipolar group ($n = 52$). The distribution of females to males was significantly lower in both carbamazepine groups compared to the lithium group (Chi-square 6.56180, *df* 2, $P = 0.0376$). The distribution of unipolar and bipolar diagnoses by

DSM-III-R were also shared rather equally between the groups (Chi-square 5.95518, *df* 2, $P = 0.5909$).

Drop outs

26 patients (31%) did not complete the 2-year trial period under prophylactic treatment. 10 patients (38.5%) dropped out within the first six weeks, 9 patients (34.6%) dropped out between weeks 7–26 and 7 patients (26.9%) dropped out between weeks 27–77. The reasons for abandoning prophylactic treatment were as follows: the decision of the patient in 50% ($n = 13$) of the cases, the patients refusal to continue prophylactic medication during a hypomanic episode in 19.2% ($n = 5$) of the cases, another physician who was consulted by the patient in 15.4% ($n = 4$), other reasons in 11.5% ($n = 3$) of all cases and, in



* from week 8 to week 104

Fig. 1. Serum levels per group (from week 8 to week 104).

TABLE 2

<i>n</i> = 84	Serum levels (from week 8 to week 104)		
	CBZ-low *	CBZ-high *	Lithium
Mean	23.00	30.49	0.66
Median	23.00	31.00	0.67
Stdev	5.73	6.08	0.15
Min	3	10	0.28
Max	41	57	1.18

* Anova: *F* 260.059; *P* = 0.000.

one patient (3.8%), because of pregnancy, in spite of the knowledge of the interaction between carbamazepine and hormonal compounds.

There was no statistical differences in the distribution of drop outs in the three treatment groups (Chi-square 2.42693, *df* 2, *P* = 0.2972).

21 of the 26 dropped out patients (80.7%) could be followed up after 2 years personally. 14 patients (66.7%) showed the same severity of their illness course compared with the 2 years before, 4 (19%) improved and 3 (14.3%) had no further episode within 2 years.

Side effects

It was remarkable that none of the patients interrupted medication because of side effects, which is most likely to occur due to the slow increase of dosage within the first 8 weeks and since both compounds were slow release preparations. More than half of the patients (51.7%, *n* = 30) on CBZ showed no side effects. The remaining patients under CBZ showed several side effects: 17.2% (*n* = 10) had problems with their thyroid gland (hypo- or hyperthyroidism). Five of them had previous treatment for the thyroid gland, and two had to undergo an opera-

tion. 6.9% (*n* = 4) suffered from a skin rash within the first 8 weeks of therapy. All four patients were sent to the Dermatology Department. Medication was continued, because there were no signs of allergic reaction. The skin rash disappeared within 2 to 3 weeks without therapeutic intervention (Three of these patients experienced several years ago allergic reactions against metals). The remaining 24.2% (*n* = 14) showed miscellaneous side effects, but none of them were continuous (detailed report with hematological and hepatic side effects is in preparation).

For the lithium group, 30.7% (*n* = 8) showed no side effects whatsoever; 26.9% (*n* = 7) had a feeling of thirst; 23% (*n* = 6) had mild polyuria; 23% (*n* = 6) showed tremor at the beginning of the therapy; and, 7.7% (*n* = 2) had to take medication for the thyroid gland.

With the regard to the safety of the two drugs we can summarize that lithium carbonate shows more frequent continuous side effects than carbamazepine, but these are mild and do not interfere with the patients' everyday life.

Serum levels

Another reason for the open design of the study was, to correct the serum levels after every visit for the planned ranges. In spite of the variety of the serum levels we tried to keep two groups with a different level of carbamazepine. Fig. 1 shows that there is an overlap between the two serum levels, but the mean (and the median) of the carbamazepine serum levels of the two groups over the 2-year period are statistically significant different (*t*-test *F* 260.059, *P* = 0.000). The carbamazepine 'low level' group showed a mean of 23 $\mu\text{mol/l}$ (median 23) and the 'high level' group a mean of 30.49 $\mu\text{mol/l}$ (median 31.00). The

TABLE 3

<i>n</i> = 58	* Total No. of episodes			** Episodes 2 years before	
	mean	stdev		mean	stdev
CBZ-low	10.00	10.67	CBZ-LOW	1.42	0.69
CBZ-high	4.72	3.39	CBZ-HIGH	1.78	1.00
Lithium	4.00	3.78	LITHIUM	1.30	0.57

Kruskall-Wallis:

* Corrected for ties: Chi-Square: 5.2608, sign.: 0.0720.

** Corrected for ties: Chi-Square: 3.7568, sign.: 0.1528.

intraindividual variations were high. The lithium group had a mean 12-h serum level of 0.66 mmol/l from week 8 to week 104 (Table 2).

Further analyses were made on the remaining 58 patients, who completed the total open 2-year observation period to compare the efficacy of 'low', versus 'high' CBZ serum level and lithium treatment group for prophylactic treatment. The three groups were comparable regarding the total number of episodes. The carbamazepin low serum group showed a higher total number of previous episodes. The three groups were also comparable regarding the number of episodes 2 years before index episode (Kruskal-Wallis 1-way Anova). As shown in Table 3, the patients of all the three treatment groups showed a relative high risk of relapse.

Efficacy

From the initial 84 patients 26 dropped out before reaching the end of the 2 years observation. As mentioned before, 13 withdraw their consent under euthymic conditions and 5 patients due to a hypomanic episode. The remainder of all

TABLE 4

n = 58	Type of relapse					
	No relapse		Outpatient relapse		Hospital admission	
CBZ-low	8	13.8%	7	12.1%	4	6.9%
CBZ-high	7	12.1%	9	15.3%	2	3.4%
Lithium	12	20.9%	7	12.1%	2	3.4%
Total	27	46.8%	23	39.5%	8	13.7%

patients under treatment is shown in Fig. 2. Of those patients, who finished the 2 years under prophylactic treatment, 27 (46.8%) had no relapse, 23 patients (39.5%) suffered from a relapse that could be treated in our outpatient clinic and 8 patients (13.7%) had to be treated as inpatients (Table 4).

With regard to the clinical judgement we already reported results for the first year (Denk et al., 1989), and for the second year (Simhandl et al., 1990; Denk et al., 1991) under prophylactic treatment (abstracts). From the above-mentioned 58 patients 4 (6.8%) showed no change in the

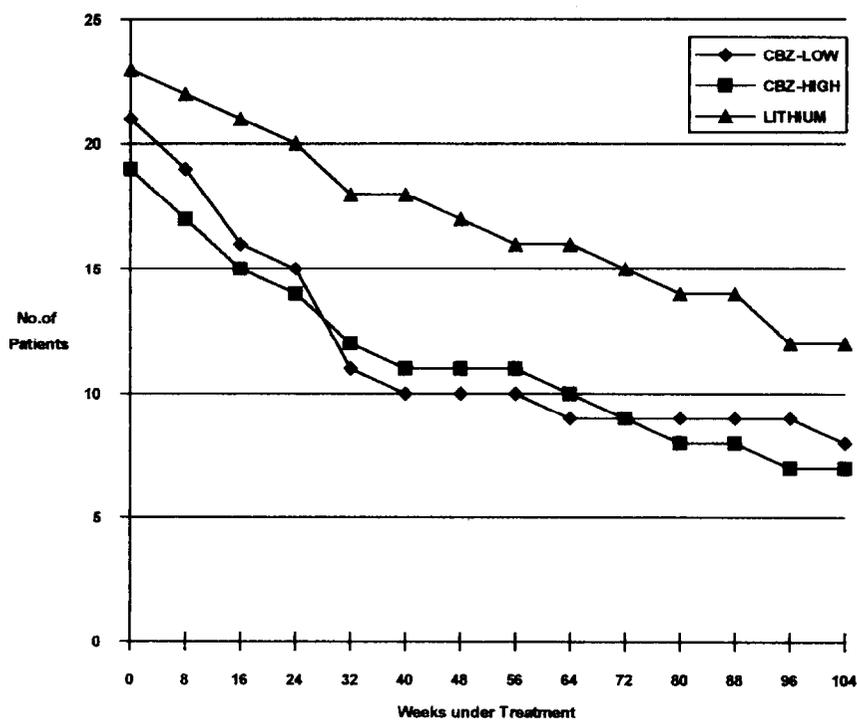


Fig. 2. Relapses; without the patients that had withdrawn IC (n = 58).

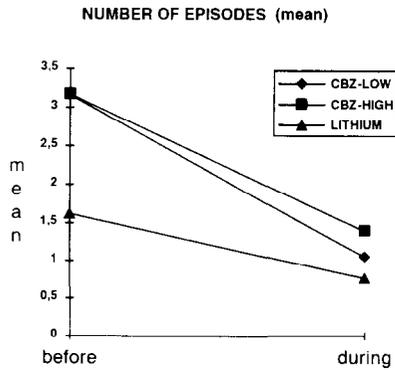


Fig. 3. Number of episodes.

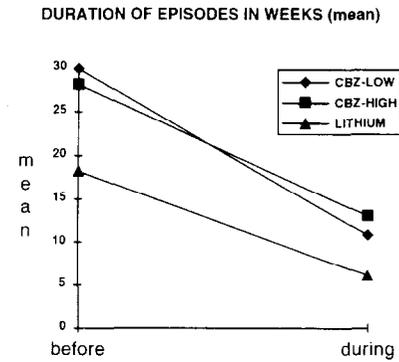


Fig. 4. Duration of episodes in weeks (mean).

course of the disease; 10 (17.2%) improved moderate in terms of shorter duration of episode or hospitalisation, or showed a better social functioning; and 44 (76%) patients improved good or very good (46.8% of them had no relapse at all). This judgement was done by two psychiatrists taking not only the relapse or recurrence into account, but judging for the whole observation period in a global way, whether there is a change in duration of episode, no more or shorter hospitalisations, change in social functioning, under the prophylactic medication

There is a marked effect of improvement, which is rather similar in all three treatment arms and is illustrated in Fig. 3 for the number of episodes and in Fig. 4 for the duration of episodes. The mean values of the number of episodes (manic and depressive included) are reduced sig-

nificantly from 3.16 in the 2 years before prophylactic treatment to 1.05 in the CBZ-low group, from 3.17 to 1.39 in the CBZ-high group and from 1.62 to 0.76 in the lithium-treated group (Wilcoxon matched pairs, two tailed probability). Table 5 also shows the reduction of hospitalisations, which reached a level of significance only for the CBZ-high group. The mean duration of episodes and vice versa the increase of the symptom free interval are altered in all groups significantly. Comparing the differences before and during treatment with the Kruskal-Wallis one way anova method indicated no advantage of one of the three treatment groups.

Looking at the unipolar ($n = 22$, 37.9%) and the bipolar ($n = 36$, 62.1%) subgroups separately (Fig. 5), there is a reduction in the duration of episodes, in the number of hospitalisations in the

TABLE 5

Number and duration of episodes, duration of symptom-free interval, number of hospitalisations (2 years before and 2 years during prophylactic treatment (mean values per group))

N = 58	CBZ-LOW		CBZ-HIGH		LITHIUM	
	before	during	before	during	before	during
No. of episodes	3.16	1.05 *	3.17	1.39 *	1.62	0.76 *
No. of hospitalisations	22.4	9.7	23.1	11.3 *	14.4	5.0
Reduction to		44%		40%		44%
Duration of episodes (in weeks)	29.9	10.8 *	28.1	13.0 *	18.2	6.1 *
Reduction to		38%		47%		35%
Duration of free interval (in weeks)	74.4	90.5 *	76.8	91.2 *	86.6	97.6 *
Reduction to		22%		19%		13%

* Wilcoxon $P < 0.05$.

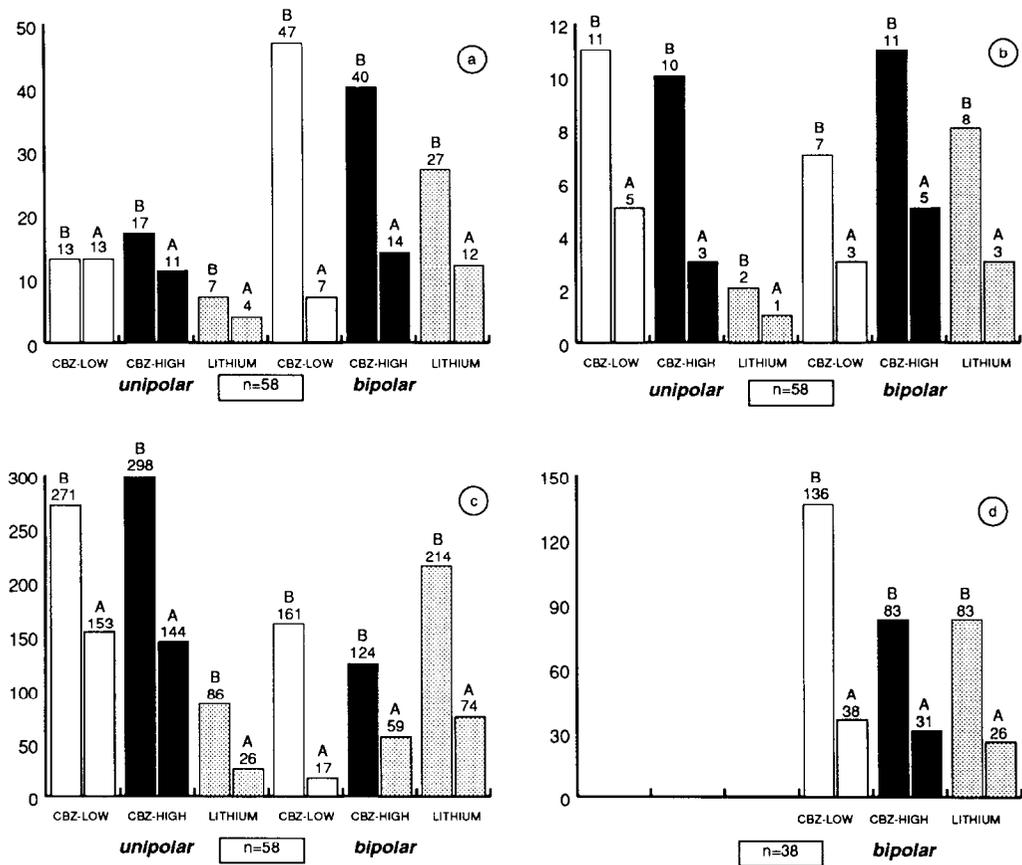


Fig. 5. Comparison of the unipolar and bipolar subgroups. Panels A to D show a comparison of the reduction 2 years before and 2 years after prophylactic treatment. White columns: CBZ-low; Black columns: CBZ-high; Dotted columns: lithium. B = before and A = after. (a) Reduction of total number of episodes. (b) Reduction of number of hospitalisations. (c) Reduction in duration of depressive episodes (No. of weeks). (d) Reduction in duration of manic episodes (No. of weeks).

duration of depressive and as well in the manic episodes of over 50% in the bipolar group, which is similar in all three treatment arms. The left top panel of Fig. 5 shows that in unipolar depressed patients there is no reduction of the number of episodes in the CBZ-low serum level group. The mean number of episodes before and during treatment with carbamazepine in a range between 15 and 25 $\mu\text{mol/l}$ is not changed. The change in the sense of a reduction in the duration of the episodes was also in the CBZ-high and in the lithium group no so decided for the unipolar group.

For the comparison between the three treatment groups the differences of the amount (sums) of weeks in episode, depression and mania, free interval and number of hospitalization over all

patients per group were built and then a Kruskal-Wallis 1-way Anova was calculated. The differences of the duration before and after treatment were made to see, whether one of the treatment groups is superior in reducing time in episodes or prolonging the time in remission. The analyses of the differences between the 2 years before prophylactic treatment and during the 2 years of prophylactic treatment distinctly show no statistically significant results. Even no trend that one of the treatment arms might be superior to another could be detected.

Discussion

In our 2 years open randomized retrospective/prospective trial we found a drop out rate of 31%

of originally 84 patients. About one third dropped out within the first 6 months. Aagaard and Vestergaard (1990) found in their 2-year prospective study with lithium patients a rate of non-adherent patients of 42.1%. A possible explanation for several dropped out patients was the fact, that in Austria because of the social security system every patient is entitled to obtain free medical treatment anywhere. This was one reason beside the ethical one not to choose a placebo-controlled group (Demisch, 1991).

The results, calculated with 58 patients retrospectively/prospectively over 2 years, regarding efficacy are very close to those mentioned studies in the introduction. Our results clearly show in spite of the lack of a placebo control group that carbamazepine is not only 'a promising alternative' but it is a definite alternative to lithium in prophylactic treatment. It can be used in patients that suffer from lithium side effects or who cannot take lithium because of contra indications and can adequately be used as a drug of first choice in patients with the indication for prophylactic treatment in bipolar disorder. All three treatment arms could reduce the time of episodes down to 35 to 47%. Also all three treatment arms did prolong the symptom free interval for 13 to 22%. In our study the lithium-treated group showed in the percentage the lowest change of reduction, but there was no significant difference in the Kruskal-Wallis test between the treatment groups. Watkins showed with a *t*-test a superiority of lithium for prolonging the time in remission. This might be due to the circumstance that the lithium group had in our sample in spite of randomisation a shorter duration of illness and the lowest mean number of episodes before prophylactic treatment. For the subgroup with unipolar recurrent depression the CBZ-low serum level group in our sample could not reduce the time of being in episode. The conclusions drawn from Demisch (1991) for a trend towards an advantage of carbamazepine in unipolar and for lithium in bipolar patients can not be confirmed by our results.

Summarizing the above-mentioned parameters, describing the alteration of the course of illness, we conclude that the low carbamazepine serum level (mean 23 $\mu\text{mol/l}$) and the high car-

bamazepine serum level (mean 30.49 $\mu\text{mol/l}$) and lithium (mean 0.66 mmol/l) are equally effective for prophylactic treatment of bipolar disorder. For relapse prevention or attenuation of a unipolar recurrent depressive course of an affective disorder the CBZ-high serum level or lithium should be preferred to a CBZ-low serum level.

Regarding the safety of the two drugs, we found that if they were used for prophylactic treatment and the dose of the slow release compounds is raised carefully at the beginning of the treatment, there would be no harmful side effects for the patient. Care has to be taken however, in recommending carbamazepine instead of lithium especially in those patients with problems of the thyroid gland. In our studies we have noticed that patients under carbamazepine may encounter problems with hyper-, hypothyroidism and goitre. We cannot say whether this is really caused by the drug. In a previous study performed by our group (Simhandl et al., 1988) we have seen an incidence of problems of the thyroid gland under long-term lithium therapy in 6.3% ($n = 265$ patients). With regard to the safety of the two drugs we can summarize that lithium carbonate shows more frequent and continuous side effects than carbamazepine, but these are mild and do not interfere with the patients' everyday life. In none of the patients side effects were the reason for dropping out.

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