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Lithium vs carbamazepine in the maintenance treatment of schizoaffective disorder: a randomised study

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Abstract In a randomised multicentre study, the prophylactic efficacy of lithium and carbamazepine was compared in schizoaffective disorder. A total of 90 ICD-9 schizoaffective patients were included in the maintenance phase (2.5 years). They were also diagnosed according to RDC and DSM-III-R and classified into subgroups. Mean serum levels were 0.58 ± 0.12 mmol/l for lithium and 6.4 ± 1.5 μg/ml for carbamazepine (mean dose 643 ± 179 mg/d). Outcome criteria were hospitalisation, recurrence, concomitant psychotropic medication and adverse effects leading to discontinuation. There were more non-completers under carbamazepine than under lithium ($p = 0.02$). Survival analyses demonstrated no significant differences between lithium and carbamazepine in treatment outcome. Patient's ratings of side effects ($p = 0.003$) and treatment satisfaction ($p = 0.02$) favoured carbamazepine. Following the RDC criteria, patients of the schizodepressive and non-classifiable type did better under carbamazepine ($p = 0.055$ for recurrence), whereas in the schizomanic patients equipotency of both drugs was found. Applying DSM-III-R, carbamazepine demonstrated a superiority in the patient group with more schizophrenia-like or depressive disorders ($p = 0.040$ for recurrence), but not in patients fulfilling the DSM-III-R criteria of bipolar disorder. Lithium and carbamazepine seem to be equipotent alternatives in the maintenance treatment of broadly defined schizoaffective disorders. However, in subgroups with depressive or schizophrenia-like features and regarding its long-term tolerability carbamazepine seems to be superior.

Key words Schizoaffective disorder · Randomised controlled trial · Lithium · Carbamazepine · Treatment outcome

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Introduction

The drug treatment of schizoaffective disorder has been subject to only few controlled studies. As a consequence, no medication is currently approved by the United States Food and Drug Administration (FDA) for the treatment of schizoaffective disorder (Keck et al. 1994).

Five controlled studies have been conducted on lithium prophylaxis in schizoaffective disorder, all with very small groups (Angst et al. 1969; Prien et al. 1974; Mattes and Nayak 1984; Placidi et al. 1986; Bellaire et al. 1990). Angst et al. (1969) compared lithium and imipramine and found a superiority of the former regarding its preventive activity. In the placebo controlled study by Prien et al. (1974), the schizoaffective subgroup, including only 6 patients, responded poorly to lithium prophylaxis as compared with manic-depressive patients. Mattes and Nayak

(1984) tested lithium vs an anti-psychotic drug. Their study sample included 14 schizoaffective patients, 13 of whom were mainly schizophrenic according to the Research Diagnostic Criteria (RDC; Spitzer et al. 1982). Their results indicate that lithium is not an adequate prophylactic treatment for this subgroup of schizoaffective patients.

The high failure rates of lithium have turned carbamazepine into a potential alternative in the prophylactic treatment of patients with schizoaffective disorder. Placidi et al. (1986) suggested that a prophylactic action of carbamazepine may exist in all forms of "atypical psychoses" transgressing the classic boundaries of the affective and schizophrenic disorders, which generally respond poorly to lithium (cf. Prien 1980). The study by Placidi et al. (1986) compared the efficacy of lithium and carbamazepine in a sample of 83 patients, among them 29 schizoaffective patients. The data indicate – without separately evaluating, however, the response of the schizoaffective group and the bipolar group – that lithium is more effective in patients with classic affective disorder, whereas carbamazepine may be more effective in patients with schizoaffective and schizophreniform features. Bellaire et al. (1990) tested lithium and carbamazepine in 109 affective patients, 17 of whom were schizoaffective. According to their data carbamazepine can be seen as a prophylactic drug equipotent to lithium in schizoaffective patients, with respect to long-term tolerability, carbamazepine demonstrated a slight superiority.

Definite conclusions about the optimal prophylactic treatment of schizoaffective disorders are not possible, not only due to the small empirical basis, but also to the different studies including very differently defined schizoaffective psychoses. Schizoaffective disorder has been classified in the literature as a subtype of schizophrenia, as a form of mood disorder, as a genuine mixed state or as a separate form of psychosis (Brockington and Leff 1979; Maj 1984b). The differing results concerning treatment may be a reflection of the intrinsic heterogeneity of schizoaffective disorders. An approach to solve this problem is to simultaneously apply several diagnostic criteria in a polydiagnostic approach. By this it is possible to single out which schizoaffective patients respond best to which kind of pharmacological treatment. Maj (1984a), who emphasises the significance of diagnostic criteria, found the response to lithium to be more pronounced in schizomanic than in schizodepressive patients. Furthermore, his results support the efficacy of lithium in prominently affective schizoaffective patients, whereas it was hardly useful in schizoaffective patients with schizophrenia-like features (cf. Müller-Oerlinghausen et al. 1990).

In 1986, a randomised prospective, *m*ulticentre study of long-term treatment of *a*ffective and schizoaffective *p*sychoses (MAP study; Greil et al. 1986, 1993) was initiated in Germany. The comparison of the prophylactic efficacy of lithium and carbamazepine in schizoaffective disorder diagnosed according to ICD-9 (WHO 1978) was one of its major goals. To account for the problem of heterogeneity in schizoaffective disorder, lithium and carbamazepine were also compared in subgroups of patients classified according to RDC (Spitzer et al. 1982) and DSM-III-R (APA 1987) using the Structured Clinical Interview (SCID, Wittchen et al. 1987).

Subjects and methods

General study design

The MAP study group consisted of nine psychiatric university hospitals in the Federal Republic of Germany (Aachen, Berlin, Düsseldorf, Heidelberg, Lübeck, München, Münster, Tübingen and Würzburg). Approvals of local ethical committees were obtained according to legal requirements. Patients were recruited while hospitalised and treated in an out-patient setting during a maintenance phase of 2.5 years. In this paper the results concerning the schizoaffective patients are presented. The results on bipolar and unipolar patients are published elsewhere (Greil et al. 1996; Greil et al., in press).

At the beginning of the study, all schizoaffective patients admitted to one of the hospitals were screened (recruitment phase). Patients who fulfilled the inclusion criteria and agreed to participate were followed in the out-patient departments (stabilisation phase). Psychotropic medication, given during the acute episode according to the free decision of the treating physician, was gradually reduced and if possible, discontinued. When the patient was in a stable condition [Global Assessment Scale (GAS) > 70; Endicott et al. 1976] for at least 2 weeks within 6 months after discharge, termination of the index episode was supposed; patients were randomised at this stage to either lithium or carbamazepine (treatment phase). This procedure aimed at a clear differentiation between the prevention of relapses and recurrences (Kupfer 1991). In a second stage of recruitment, randomisation was also allowed during acute-phase treatment, as the study protocol turned out to be unrealistic concerning the course of affective and schizoaffective disorders and clinical practice. In sum, 36% of the patients had been randomised during hospitalisation, but in these cases the observation period of 2.5 years was started all the same after the individual patient had been stabilised. The average duration of the stabilisation phase was 116 days (median 96 days).

Patients

Patients included had to fulfil the following criteria:

1. Current episode of schizoaffective disorder according to ICD-9 (295.7; WHO 1978)
2. At least one former episode during the 3 years preceding the index episode (Angst 1981)
3. No physical disability sufficient to preclude treatment with lithium or carbamazepine
4. No preventive treatment immediately before onset of the present episode
5. Age between 18 and 65 years
6. No alcohol or drug abuse
7. Informed consent

A total of 110 schizoaffective patients fulfilled the inclusion criteria and could be included. Aside from statistically significant, but clinically negligible, lower GAS scores in the study patients, no substantial differences between study and non-study schizoaffective patients were found (Greil et al. 1993). A total of 20 patients could not be stabilised or dropped out of the study for other reasons. A total of 90 patients reached the maintenance phase, i.e. the treatment period. No relevant differences were found between patients reaching and those not reaching the maintenance phase in terms of sociodemographic and clinical variables (not shown). According to anamnestic data, 69% of the patients had never received prophylactic treatment before.

Of the patients, 82% fulfilled the RDC criteria (Spitzer et al. 1982) of a Schizoaffective Disorder, 53% of them with manic type

and 38% with depressed type at the index episode, 9% were not classifiable in this regard. Of the RDC schizoaffective patients, 84% were predominantly affective, and 16% predominantly schizophrenic in the index phase. Using SCID (Wittchen et al. 1987), the following DSM-III-R-diagnoses were established: 19% of the study patients presented Schizoaffective Disorder, 10% Major Depressive Disorder, recurrent, 47% Bipolar Disorder, 15% Bipolar Disorder Not Otherwise Specified (NOS), 1% Schizophrenia, 1% Schizophreniform Disorder and 5% were diagnosed as Psychotic Disorder Not Otherwise Specified (NOS).

Randomisation and study medication

Randomisation lists were produced for each centre in advance. The lists were kept at the coordinating study centre in Munich, and the psychiatrist in charge of a study patient was informed about the treatment group allocation by phone.

During the maintenance phase patients' serum levels (12 h after drug intake) had to be adjusted to 0.6–0.8 mmol/l for lithium and to 4–12 µg/ml for carbamazepine. Additional medication was accepted, if necessary, and documented.

Assessments

Various observer ratings of psychopathology were carried out by extensively trained psychiatrists and patients completed several self-ratings (see Greil et al., 1996). Somatic complaints, course of illness before index episode and information on other biographic, social and clinical aspects were documented. Unwanted side effects were assessed by the physician on a four-point scale. Patients rated side effects and satisfaction with treatment on a 100-mm Visual Analogue Scale (VAS; Aitken 1969).

Main examinations with all assessments were routinely performed at study entry and 1, 2 and 2.5 years after treatment onset, and a selected part of the measurements was repeated during outpatient appointments in-between. Additionally, laboratory parameters, including lithium and carbamazepine serum levels, were determined at each contact. Psychotropic co-medication (i.e. antidepressants, neuroleptics, benzodiazepines) was converted into values of defined daily doses (DDD, Nordic Council on Medicines 1985), in order to make the amount of different drugs comparable. The DDD is a standard dose agreed upon, e.g. by the WHO Drug Utilisation Research Group (DURG), and often is close to the average daily dose as recommended by the manufacturer for common indications.

During the first 3 months of the study, patients were seen in the out-patient clinic every 4 weeks, and later every 8–12 weeks. In cases of severe side effects and affective or psychotic symptoms, patients were seen in shorter intervals. At each visit the clinical course was retrospectively assessed for every week on a four-point scale using the Morbidity Index (Coppen 1976). Psychopathology was rated for every month on a six-point scale (1 = no disturbance to 6 = extremely severe recurrence) by physicians trained in applying RDC criteria.

Study monitoring

During the whole maintenance phase, regular study monitoring of all participating centres according to the principles of "Good Clinical Practice" (GCP) was performed by specialised members of the co-ordination centre in Munich. Various strategies, e.g. comparison of medical reports, observer ratings and self-ratings, were used to control the validity and inner consistence of the data.

Evaluation of outcome

As several definitions of treatment failure are presented in the literature, different dimensions of outcome were considered:

1. Admission to a psychiatric hospital
2. Recurrence [psychopathology rating of 5 (recurrence) or 6 (extremely severe recurrence)]
3. Prescription of concomitant psychotropic medication (antidepressants and/or neuroleptics) for at least 6 months
4. Severe side effects, prompting discontinuation of treatment

By combining these dimensions, four definitions of treatment failure were formulated for statistical analysis: (a) hospitalisation; (b) recurrence; (c) recurrence and/or concomitant psychotropic medication; (d) recurrence and/or concomitant psychotropic medication and/or side effects.

Lithium and carbamazepine were also compared within diagnostic subgroups. Therefore, post hoc diagnostic categories were formed based on the available polydiagnostic data. The patients were classified (a) according to RDC into a "schizoaffective depressive" subgroup, including also the non-classifiable patients, and a "schizoaffective manic" subgroup, both referring to the symptoms of the index episode, and (b) according to DSM-III-R (SCID) into "Bipolar Disorder" and "Other Disorders" (Bipolar Disorder NOS, Major Depression, Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Psychotic Disorder NOS) referring to the lifetime course.

Statistical analysis

Treatment groups and subgroups were compared by survival analysis (Kaplan-Meier method; Kaplan and Meier 1958), based on intent-to-treat data (ITT). Survivor functions were tested for equality by the Tarone-Ware statistics (Tarone and Ware 1977). Failure rates of completers (according to protocol) were compared by Fisher's exact test. The amount of concomitant medication (DDD) was compared by *t*-test, and unwanted side effects by χ^2-test and Kolmogorov-Smirnov test. A *p*-value of < 0.05 (two-tailed) was considered to be statistically significant.

Results

Study patients and non-completers

Of the 90 study patients, 43 had been allocated to lithium and 47 to carbamazepine. No significant differences regarding gender, age, number of previous episodes, attempted suicides, severity of symptomatology and other clinical and sociodemographic characteristics were observed between the treatment groups (see Table 1).

21 (23%) of the 90 patients did not complete the study for various reasons (see Table 2) without any recurrence having occurred.

There were more non-completers under carbamazepine (15) than under lithium (5; $p = 0.02$, Fisher's exact tests). Except for a tendency of the non-completers to exhibit more previous episodes, no differences in the sociodemographic and clinical variables between completers and non-completers were observed.

Dosage and serum levels

Dosage and serum levels were within the intended range. Average dose was 28 ± 8 mmol/day for lithium (average serum level 0.58 ± 0.12 mmol/l) and 643 ± 179 mg/day for carbamazepine (average serum level of 6.4 ± 1.5 µg/ml). These figures represent average values obtained be-

Table 1 Demographic and clinical characteristics of the included patients. GAS Global Assessment Scale

	Lithium	Carbamazepine
n	43	47
Gender (% female)	67	79
Age (years mean ± SD)	35 ± 9	35 ± 10
Marital status (%)		
Never married	42	43
Married	37	38
Separated/divorced	21	17
Widowed	–	2
Years of education (%)		
≤ 9 (elementary school)	33	36
10 (secondary school)	30	23
13 (graduate)	37	40
Age at onset (years, mean ± SD)	26 ± 7	26 ± 8
% of patients with positive family history (affective disorders)		
In first-degree relatives	21	22
In other relatives	10	7
Suicide attempts (% patients)		
None	60	56
1	26	28
2 or more	14	16
Episodes of illness (%)[a]		
2	14	21
3–5	47	43
6 or more	40	36
Hospitalisation (%)[a]		
1–2	12	11
3–6	72	62
7 or more	17	28
GAS score (mean ± SD)	79 ± 10	78 ± 9

[a] Includes index episodes

Table 2 Reasons for non-completion

Reasons for non-completion	Lithium ($n = 43$)	Carbamazepine ($n = 47$)
Treatment-related reasons:		
Unwanted side effects[a]	1	4
Persistent disturbances[b]	–	2
Protocol violators[c]:		
Contraindication[d]	–	2
Other reasons[e]	4	7
Total[f]	5	15

[a] For further details see Table 8
[b] Discontinuation by the physician due to long-term need of concomitant medication
[c] The difference in protocol violation was not significant ($p = 0.24$)
[d] Pregnancy
[e] This category comprises reasons for non-completion not related to treatment, e.g. external circumstances or decision against further treatment without clear reasons
[f] $p = 0.0242$ according to Fisher's exact test

tween 2 months after onset of treatment and either termination after 2.5 years or discontinuation for other reasons.

Treatment outcome

Figures 1–4 present the survivor functions of the 90 schizoaffective patients according to the different definitions of treatment failure mentioned previously.

Table 3 shows the corresponding statistics according to intent-to-treat analyses, i.e. all patients who entered the

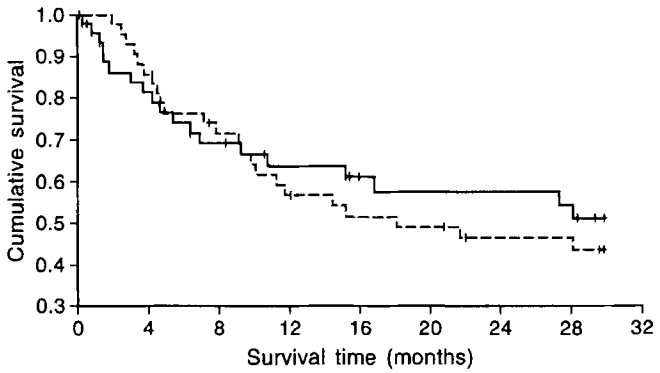

Fig. 1 Survivor functions (Kaplan-Meier estimate); cumulative proportion of patients not fulfilling the failure criterion, for both treatment groups and different outcome criteria: hospitalisation. *Solid line* carbamazepine; *dotted line* lithium; *tick on lines* cases censored

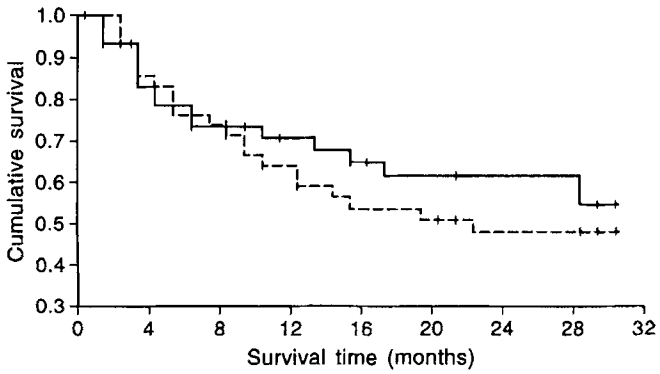

Fig. 2 Same as Fig. 1: recurrence

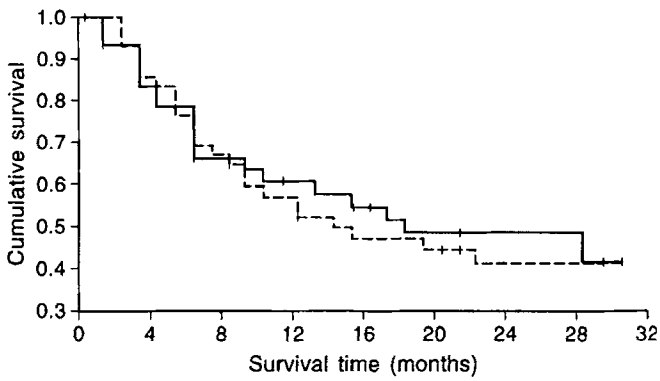

Fig. 3 Same as Fig. 1: recurrence/concomitant medication

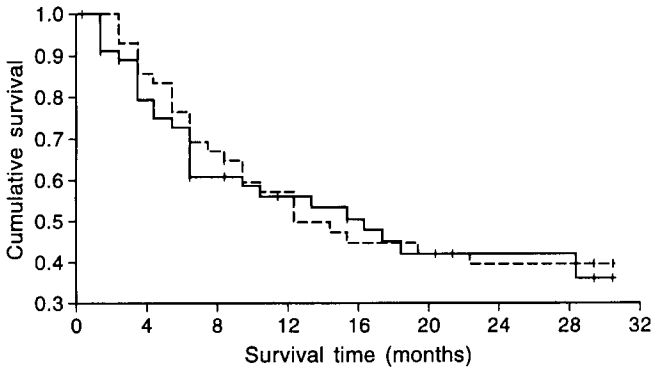

Fig. 4 Same as Fig. 1: recurrence/concomitant medication/side effects

Table 3 Survival analyses of differences between treatment groups (intend to treat, ITT) for various failure criteria

Failure criteria	p^b	Events[c]	
		Li ($n = 43$)	Cbz ($n = 47$)
Hospitalisation[a]	0.760	23	19
Recurrence	0.582	21	17
Recurrence and/or concomitant medication	0.881	24	22
Recurrence and/or concomitant medication and/or side effects	0.726	25	26

[a] There are more hospitalisations than recurrences, explained by the fact that there were hospitalisations during which the psychopathology was rated as only subclinical episode
[b] Tarone-Ware
[c] Indicates number of failures

Table 4 Frequencies of treatment failures and completers (according to protocol) in treatment groups (P-value based on Fisher's exact test)

Failure criteria	Lithium		Carbamazepine		p
	Failues/ completers[a]	%	Failures/ completers	%	
Hospitalisation	23/38	61	19/34	56	0.81
Recurrence	21/37	57	17/32	53	0.81
Recurrence and/or concomitant medication	24/38	63	22/34	65	1.00
Recurrence and/or concomitant medication concomitant medication and/or side effects	25/39	64	26/38	68	0.81

[a] Differences in number of completers are due to the fact that, depending on the criterion, dropping out may have occurred before *or* after the "failure", because patients were not necessarily excluded after they had met a failure criterion

maintenance phase were included in the analysis. For none of the failure criteria significant differences between the two treatment regimens were observed.

In order to enhance the comparability with other studies, the frequencies of treatment failures in relation to those who completed the study were analysed (see Table 4). For example, regarding the failure criterion "recurrence", 21 of 37 completers in the lithium group and 17 of 32 completers in the carbamazepine group were treatment failures (57% vs 53%). As in the survival analyses, the statistical testing revealed no treatment-related differences.

Within the 74 patients diagnosed by RDC as "Schizoaffective", in the subgroup of patients with "Schizoaffective Disorder, Manic Type", survival analyses showed no statistically significant differences between the two drugs. Within the subgroup "Schizoaffective Disorder, Depressed Type", a statistically significant superiority of carbamazepine was found for the treatment failure criterion "hospitalisation" ($p = 0.019$), a tendency for "recurrence" ($p = 0.055$) and the latter criterion combined with "concomitant medication" ($p = 0.053$; see Table 5). Similar results were observed when excluding the 7 non-classifiable patients from the analysis (not shown).

The assessment regarding manic or depressed subtype was made in the index phase of the respective patient. Correlation analyses, based on anamnestic data, revealed that the schizoaffective depressed patients were significantly more depression prone than the mania-prone schizoaffective manic group ($p < 0.001$).

Among the 37 patients with the DSM-III-R diagnosis of a "Bipolar Disorder", patients under lithium showed comparable response to those under carbamazepine. In the subgroup of patients with other diagnoses (Bipolar Disorder NOS, Major Depression, Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Psychotic Disorder NOS) treatment with carbamazepine obtained non-significantly ("hospitalisation", $p = 0.056$) and significantly better results ("recurrence", $p = 0.040$; see Table 6).

Regarding the different subgroups according to RDC ("Schizoaffective Manic" and "Schizoaffective Depressive") and DSM-III-R ("Bipolar Disorder" and "Other Disorders"), only a slight relationship (phi = 0.23915, $p = 0.058$; χ^2-test) was found. This indicates that the results applying RDC and DSM-III-R subgroups do not refer to the same patients.

Concomitant medication

The frequency of patients taking concomitant psychotropic medication for 6 months or more (13 patients) did not differ significantly between the two treatment groups (lithium 7 vs carbamazepine 6). Three lithium and 5 carbamazepine patients were classified as treatment failures due to continuous concomitant psychotropic medication, and the others had already been considered as treatment failures because of a recurrence.

The detailed analysis of patients' concomitant medication (antidepressants, neuroleptics, benzodiazepines) at the main examination days after 1, 2 and 2.5 years is based on the defined daily dose (DDD; see Table 7). For none of the

Table 5 Survival analyses for differences between treatment groups (ITT) in RDC subtypes of schizoaffective disorder

Failure criteria	Events					
	Schizomanic (n = 39)			Schizodepressive[b] (n = 35)		
	Li (n = 16)	Cbz (n = 23)	p[a]	Li (n = 19)	Cbz (n = 16)	p[a]
Hospitalisation	8	13	0.229	12	2	0.019
Recurrence	7	11	0.396	11	3	0.055
Recurrence and/or concomitant medication	9	14	0.252	12	4	0.053
Recurrence and/or concomitant medication and/or side effects	10	15	0.248	12	7	0.351

[a] Tarone-Ware
[b] This subgroup includes 7 patients not classifiable as truly schizomanic or schizodepressive

Table 6 Survival analyses for differences between treatment groups (ITT) regarding different DSM-III-R diagnoses within the group of ICD-9 schizoaffective patients

Failure criteria	Events					
	Bipolar disorder (n = 37)			Other disorders[b] (n = 41)		
	Li (n = 19)	Cbz (n = 18)	p[a]	Li (n = 21)	Cbz (n = 20)	p[a]
Hospitalisation	11	11	0.773	10	2	0.056
Recurrence	10	10	0.997	10	2	0.040
Recurrence and/or concomitant medication	12	12	0.972	11	5	0.236
Recurrence and/or concomitant medication and/or side effects	12	13	0.913	12	7	0.502

[a] Tarone-Ware
[b] Other disorders found in study sample using SCID were "Bipolar Disorder NOS", "Major Depression", "Schizophrenia", "Schizophreniform Disorder", "Schizoaffective Disorder", "Psychotic Disorder NOS"

Table 7 Concomitant medication during lithium and carbamazepine medication at the main examinations. DDD defined daily dose; AM arithmetic mean

DDD	After 1 year		After 2 years		After 2.5 years	
	Li (n = 35)	Cbz (n = 29)	Li (n = 29)	Cbz (n = 22)	Li (n = 25)	Cbz (n = 22)
% none	60	72	69	77	56	64
AM	1.22	1.10	1.25	0.72	0.90	1.25
± SD[a,b]	± 1.07	± 0.89	± 1.02	± 0.30	± 1.03	± 1.31

[a] Only patients receiving concomitant medication
[b] Not significant by using the t-test for comparison of lithium vs carbamazepine

Table 8 Side effects leading to treatment discontinuation

Patient	Month	Carbamazepine	Patient	Month	Lithium
20836	2	Exanthema	10024	3	Folliculitis, photosensitisation, pruritus
62654	4	Exanthema			
70025	1	Nausea, diarrhoea			
90506	1	Exanthema, pruritus			

main examination days were significant differences in the DDD between the two treatment groups observed. 53% of the patients received no additional psychotropic drug on any of the main examination days.

Unwanted side effects

Side effects leading to discontinuation of treatment were slightly (n.s.) more frequent under carbamazepine than under lithium, mostly due to allergic reactions such as cutaneous manifestations. They occurred within the first months of medication (see Table 8).

There was no significant difference in the overall assessment of subjective side effects between treatment groups; however, 2.5 years after treatment onset, 41.7% of the lithium patients felt impaired by slight and moderate side effects compared with 27.3% of the carbamazepine group (see Table 9).

Side effects were also analysed in detail, excluding data obtained during the first 6 months after start of study treatment, in order to avoid overrepresentation of initial side effects. Significant differences were all in favour of carbamazepine. More patients under lithium than under carbamazepine suffered at least once from tremor (lithium vs carbamazepine, 40 vs 5%; $p < 0.001$, χ^2-test), increased appetite (50 vs 21%; $p = 0.008$), dryness of the mouth (29 vs 8%; $p = 0.018$), feeling of weakness (40 vs 18%; $p = 0.043$), fatigue (55 vs 24%; $p = 0.005$), polydipsia (55 vs 0%; $p < 0.000$), polyuria (37 vs 5%; $p = 0.001$), sudoresis (45 vs 16%; $p = 0.006$), weight gain (61 vs 24%; $p = 0.001$), disturbances of concentration (68 vs 40%; $p =$

Table 9 Overall assessment of subjective side effects reported by patients under lithium and carbamazepine

NOTE: No significant differences at any examination day by using Kolmogorov-Smirnov test

Complaints	1 year after start		2 years after start		2.5 years after start	
	Li (n = 35)	Cbz (n = 31)	Li (n = 29)	Cbz (n = 24)	Li (n = 24)	Cbz (n = 22)
None (%)	51.4	77.4	48.3	75	58.3	72.7
Slight (%)	34.3	22.6	37.9	25	29.2	22.7
Moderate (%)	14.3	0	10.3	0	12.5	4.5
Severe (%)	0	0	3.4	0	0	0

0.01), retardation of thought processes (34 vs 13%; p = 0.03) and difficulties of falling asleep (55 vs 21%; p = 0.002).

Patients' ratings of side effects and satisfaction with treatment

Two and a half years after onset of the maintenance phase, patients' satisfaction (100-mm visual analogue scales) concerning side effects and treatment in general was significantly higher in the carbamazepine group than in the lithium group (lithium vs carbamazepine 74 ± 23 vs 92 ± 9, p = 0.003 for side effects, and 76 ± 24 vs 90 ± 11, p = 0.016 for treatment in general, t-tests).

Suicidal behaviour

During the treatment period, there was no suicide; 4 patients, however, attempted suicide. All patients had been on carbamazepine at the time of the suicide attempt (regarding suicidal behaviour in the MAP study generally, see Thies-Flechtner et al. 1996).

Discussion

The present prospective study compares the prophylactic efficacy of lithium and carbamazepine in schizoaffective disorder and to our knowledge, has used the largest number of patients thus far. Patient recruitment was carried out carefully (Greil et al. 1993), so that the sample is representative for hospitalised ICD-9 schizoaffective patients in need of prophylactic treatment. Randomisation was accomplished successfully, as can be concluded from the similarity in basic characteristics of treatment groups at study onset. In order to ensure that outcome of prophylaxis, and not of acute treatment, was investigated, maintenance treatment was started only after the patients were in a stable condition. The trial also lasted long enough to assess true prophylactic efficacy.

For none of the applied outcome criteria differences between lithium and carbamazepine were found. This is in contrast to our findings in bipolar patients where lithium was somewhat superior to carbamazepine (Greil et al. in press). Depending on the failure criterion, between 53% and 68% of patients did not respond satisfactorily to the prophylactic medications. This finding corresponds to the observation that schizoaffective disorders, similar to other atypical psychoses, benefit less from prophylactic treatment with lithium than "pure" affective disorders (Brockington and Leff 1979; Prien 1979). The study sample was rather "affective" than "schizophrenic", and the prevailing opinion regarding this feature is that the more predominant the affective component, the higher the efficacy of lithium therapy (Prien 1979; Maj 1984a; Maj 1988; Placidi et al. 1986). Hence, better results in favour of lithium could have been expected. On the other hand, a general superiority of carbamazepine in mood disorders with schizoaffective features, as supposed by Placidi et al. (1986), was not observed either.

Further subgrouping of the sample could provide a more outlined picture. Schizoaffective disorder is considered to be a diagnosis comprising a heterogeneous patient group, especially when using the broad definition provided by ICD-9. At the time of study onset, Anglo-American research emphasised the classification of schizoaffective disorder into schizoaffective depressed and schizoaffective manic types according to RDC (Brockington et al. 1980a, b; Lenz and Wolf 1986). According to Lenz and Wolf (1986) schizoaffective manic patients are supposed to be more homogeneous and to resemble bipolar patients more regarding basic characteristics, as compared with schizoaffective depressed patients, who form a heterogeneous clinical sample. To examine more closely which patients respond to which treatment, in the present study patients were categorised according to RDC and DSM-III-R using SCID. This additional subgrouping revealed no significant differences between the two treatment regimens in the schizoaffective manic group (RDC). However, in the schizoaffective depressed group including more heterogeneous patients, those under carbamazepine did better than lithium patients. This is in accordance with Maj (1984a, 1988), who suggested that lithium is relatively ineffective in schizoaffective patients diagnosed as schizodepressive.

Applying DSM-III-R criteria only 19% of the study patients were diagnosed as Schizoaffective Disorder. According to DSM-III-R this diagnostic category should be considered only for a residual group of patients; the majority meet the criteria of other diagnoses. When separately evaluating patients with "Bipolar Disorder" according to DSM-III-R and the group of patients with heterogeneous disorders such as "Bipolar Disorder NOS", "Major Depression", "Schizophrenia", "Schizophreniform Disorder", "Schizoaffective Disorder" and "Psychotic Disorder NOS", again the results support the hypothesis of a different treatment

response. In the more homogeneous bipolar group, lithium and carbamazepine exert a similar prophylactic capacity. In the remaining patients, characterised by diagnostic heterogeneity, carbamazepine is superior to lithium concerning recurrences and hospitalisation as outcome criteria. The results also support the findings of Placidi et al. (1986), showing a comparable prophylactic effect of lithium and carbamazepine in disorders with strong affective colouring, but a superiority of carbamazepine in several more or less "atypical" psychoses, possibly explained by a broad-spectrum activity of this drug. In the present study, the different subgroups according to RDC and DSM-III-R, respectively, did not reveal a strong relationship; in particular the schizomanics were not the same as the DSM-III-R bipolar patients.

The findings presented in this paper are supported, when the pre-treatment and treatment periods are compared. Only in the schizodepressive group according to RDC, and in the group with depressive and schizophrenia-like colouring according to DSM-III-R, could a clear-cut efficacy of carbamazepine, but not of lithium, be detected (to be published elsewhere).

Long-term tolerability is an aspect that could facilitate the decision between two prophylactic drugs: in the present study, carbamazepine, as compared with lithium, caused less side effects – disregarding initial effects prompting discontinuation in a few patients – and went along with a higher level of patients' satisfaction with treatment. Suicidality, on the other hand, seems to be less favourably influenced by carbamazepine than by lithium: in the lithium group, no suicide or suicide attempt occurred, whereas 4 patients attempted suicide in the carbamazepine group.

Further comparative research is needed to clarify the respective advantages and disadvantages of both prophylactic agents. The polydiagnostic results of this study, however, may offer indications regarding the often-discussed problem of pharmacological response in a patient collective with such high non-response rates as in schizoaffective disorder.

Conclusion

The results of the present study indicate a similar prophylactic response to lithium and carbamazepine with respect to recurrences, hospitalisation and need for concomitant psychotropic medication in schizoaffective patients when using a broad definition of this disorder as provided by ICD-9. However, regarding side effects, long-term tolerability and subjective satisfaction with treatment, carbamazepine seems to be superior to lithium. The classification of schizoaffective patients into "schizomanic" and "schizodepressive" patients (RDC) as well as into bipolar patients and patients with depressive or schizophrenia-like features (DSM-III-R), supports the prevailing opinion of a superiority of carbamazepine in the prophylactic treatment of atypical affective syndromes. It also sheds light on the intrinsic heterogeneity of schizoaffective disorder.

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