Carbamazepine versus Lithium in the Prophylaxis of Bipolar Affective Disorders. A Randomised, Double-Blind 1-Year Study in 168 Patients.

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Introduction

The short-comings of lithium in the long-term prophylaxis of bipolar affective disorders have turned the attention of research to alternatives such as the anticonvulsants carbamazepine (CBZ) and valproate for some years now.

This paper presents a 1-year double-blind study of the slow-release carbamazepine preparation Timonil® retard versus lithium for the prophylaxis of bipolar affective disorders carried out in 168 patients in seven Hungarian psychiatric units from 1994 to 1997. Its purpose was to clarify the value of CBZ's efficacy in comparison to lithium as the available studies have conflicting results and methodological problems.

Despite being planned before the meta-analysis of Dardennes et al. (1995), this study fulfills a majority of the criteria set out in their quality inventory.

To our knowlegde, we are presenting the first study using slow-release preparations of lithium carbonate and CBZ.

Patient Selection Criteria

Patients had to fulfil the later major criteria:

(1) one or more manic and depressive episodes according to DSM-III-R,
(2) score of < 4 at the Hamilton depression scale
(3) score of < 3 at the Bech-Rafaelsen mania scale,
(4) no prior prophylactic medication or lithium as a prophylactic medication,
(5) no other current psychotropic medication,
(6) age between 18 and 70 years
(7) no clinically relevant somatic pathology
(8) no contraindications for therapy with CBZ or lithium
(9) written informed consent,
(10) for patients on lithium: medico-ethical appropriateness to change the patients' medication.

Study Design

The design was adapted from Coxhead et al. (1992). It was conducted with two parallel groups.

To avoid initial adverse effects of CBZ and lithium withdrawal events in patients previously on lithium and randomised to CBZ, the following procedere was applied for the first 14 days using a double-dummy technique: (a) prior lithium patients received either CBZ in a slowly increasing and lithium in a slowly decreasing dose or 900 mg lithium alone, (b) prior drug-naïve patients were given CBZ or lithium in a slowly increasing dose.

After that initial phase the patients received individually tailored doses for one year. Drug serum levels were monitored by a blind observer. The psychic status of the patients was evaluated monthly by the Hamilton depression scale (17 items), the Bech-Rafaelsen mania scale, the respective DSM-III-R criteria, and visual analogue scales.

Methods of Evaluation

The first recurrence of an affective episode counted as a terminal event. No rescue medication was allowed. A survival rate in the CBZ group of not less than 15% as compared with lithium would be assumed as non-inferior.

The efficacy of the test drugs was assessed by comparison of the survival functions via log-rank test (Mantel-Cox) with a type I error of 5% (one sided). For non-inferiority testing, 95% confidence interval were calculated.

Rates of completion, withdrawal due to adverse events and other reasons were also evaluated.

The current presentation is in so far preliminary, as not all data have been entered twice into the data set and as several queries related to secondary data (e.g. laboratory parameters) are still pending.

Population

	CBZ	Lithium	Total
N	84	84	168
Male/female	29/55	31/53	60/108
Age in years*	44.1 [18-67]	44.7 [18-69]	44.4 [18-69]
Weight in kg*	72.4 [43-114]	71.1 [47-103]	71.7 [43-114]
Known prior manic episodes*	4.5 [1-20]	4.6 [1-18]	4.5 [1-20]
Known prior depressive episodes*	4.8 [0-25]	4.4 [1-21]	4.6 [0-25]
Prior treatment with lithium	45 (53.6%)	40 (47.6%)	85 (50.6%)

** mean and minimum - maximum*

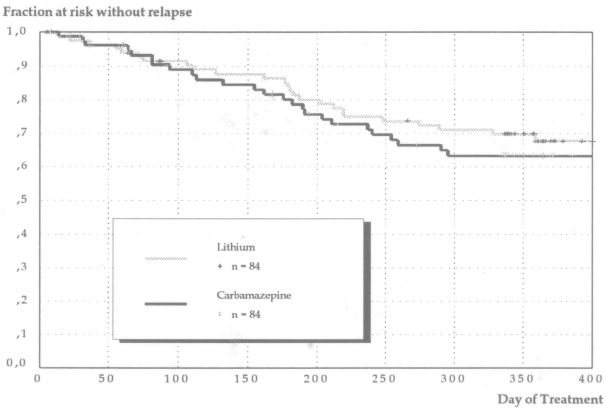
Treatment Data

During the first 14 days, patients received a fixed medication of the trial medication according to their pre-treatment status resulting in either 900 mg CBZ or 900 mg lithium at day 14.

The average doses of trial medication after day 14 were 835 mg/day for CBZ (minimum 361 mg/day; maximum 1207 mg/day) and 888 mg/day for lithium (minimum 459 mg/day; maximum 1641 mg/day).

The majority of patients did not receive any co-medication during the study. The co-medication taken was distributed even between the treatment groups and consisted mainly of short-time sleep medication, antibiotics, gastrointestinal and cardio-vascular agents.

Survival Curves and Censored Patients (Intent to Treat)



Reasons for study termination

	CBZ		Lithium		Total	
Regular completion of trial	40	47.6%	53	63.1%	93	55.4%
Relapse	25	29.8%	25	29.8%	50	29.8%
Adverse events	12	14.3%	5	6.0%	17	10.1%
Non-compliance	7	8.3%	1	1.2%	8	4.8%
Technical reasons	1	1.2%	0	0.0%	1	0.6%
Total	84	100.0%	84	100.0%	168	100.0%

Results

Efficacy

A total of 168 patients were randomised to treatment (84 to CBZ and 84 to CBZ). Differences in demographic profiles were not clinically relevant among the two groups. The Kaplan-Meier survival curves are shown in the left hand figure, while completion and withdrawal rates are shown in the table below the figure.

Rates of treatment failure with regard to efficacy were similar: 59 patients (70.2%) of each group experienced no recurrence of an affective episode. All patients were included into the statistical evaluation (intention-to-treat principle). While testing for non-inferiority, a 95% confidence interval between 61.51% and 77.71% for the survival of patients treated with CBZ was found. The 15% margin of non-inferiority is 55.2% and thus lower than the lower limit of the calculated 95% confidence interval for the CBZ group.

Safety

All adverse events (AEs) registered during the trial were known for the trial drugs. Twelve patients of the CBZ group and 5 patients of the lithium group had to be withdrawn due to AEs. Skin reactions were the majority of AEs leading to termination of the trial in the CBZ group, whereas mainly gastro-intestinal disturbances caused the termination of patients of the lithium group.

55 patients (65.5%) of the CBZ group and 59 patients (70.2%) of the lithium group experienced no AEs. Disturbances of the nervous system were seen in 18 patients (10.7%) followed by gastro-intestinal, hepatic and psychiatric disturbances and disturbances of the general well-being, each of those seen in 9 patients (5.4%). There was no difference between the distribution of those more common AEs among the treatment groups.

Conclusion

The lower limit of the 95% confidence interval for the CBZ group was higher than the margin of the 15% range for the corresponding rate for the lithium group (61.51% versus 55.2%). Even restricting the margin to 10% would not result in potential inferiority of CBZ.

CBZ represents therefore an effective alternative to lithium when treating patients suffering from bipolar affective disorders. Non-inferiority could be established within a 15% interval.

between 15 and 60 mg a day. 38.5% of the patients got 30 mg/day, 32.7% 45 mg/day. 76% of the patients showed a primary response of the leading depressive symptomatology. In 24% mitrazapine effectively was given as part of a combined therapy in difficult cases of antidepressants non-response. The only side-effect, which could be seen, wa a moderate and short timed dizziness especially during the morning hours in 15% of all cases.

As a result of our casuistic views we think, that mirtazapine has a good efficacy on depressive syndromes of the age with significant less side effects, especially in comparison to tricyclic antidepressants.

P.1.130 Carbamazepine versus lithium in the prophylaxis of bipolar affective disorders. A randomised, double-blind 1-year study in 168 patients

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A 1-year double-blind study of slow-release carbamazepine (Timonil ® retard) versus lithium for the prophylaxis of bipolar affective disorders was carried out in 168 patients in six Budapest psychiatric units from 1994 to 1997. Its purpose was to clarify the value of carbamazepine's [CBZ] efficacy in comparison to lithium as the available studies have conflicting results and methodological problems[1,2]. This trial is – to our knowledge – the first studying slow-release CBZ versus slow-release lithium.

Patients had to fulfil the later major criteria: (a) one or more manic and depressive episodes according to DSM-III-R, (b) scores of <4 at the Hamilton depression scale and <3 at the Bech-Rafaelsen mania scale, (c) lithium as a prophylactic agent or no prophylactic medication, (d) no other psychotropic medication, (e) written informed consent, and (f) for patients on lithium: medico-ethical appropriateness to change the patients' medication.

The design of trial was adapted from Coxhead et al.[2] It was conducted with two parallel groups. To avoid initial adverse effects of CBZ and lithium withdrawal events in patients previously on lithium and randomised to CBZ, the following procedure was applied for the first 14 days using a double-dummy technique: (a) prior lithium patients received either CBZ in a slowly increasing and lithium in a slowly decreasing dose or 900 mg lithium alone, (b) prior drug-naive patients were given CBZ or lithium in a slowly increasing dose. After that initial phase the patients received individually tailored doses. Drug serum levels were monitored by a blind observer. The psychic status of the patients was evaluated monthly by the Hamilton depression scale (17 items), the Bech-Rafaelsen mania scale, the respective DSM-III-R criteria, and a visual analogue scale.

The efficacy of the test drugs will be assessed by comparison of the survival functions via log-rank test (Mantel-Cox) with a type I error of 5% (one sided). The first recurrence of an affective episode (or the withdrawal of a patient from the study) counts as a terminal event. No rescue medication was allowed. A survival rate in the CBZ group of not less than 15% as compared with lithium would be assumed as non-inferior.

150 patients have completed the study so far. The remaining 18 patients will be finished until July 1997. The following results can be reported for the 150 completers: 76 patients (50.7%) had no recurrence of an affective episode during the study. 25 (16.7%) and 24 (16.0%) dropped out for mania or depression, respectively. In 16 patients (10.7%) the trial had to be stopped due to adverse events and in 9 (6.0%) due to non-compliance. Results for either drug will be reported in the presentation after de-blinding.

The overall survival rate for CBZ and lithium combined is so far comparable to other studies[1,2]. Due to sample size and robust design this trial shall contribute remarkably to our knowledge about the comparative efficacy of CBZ and lithium in the prophylaxis of bipolar affective disorders.

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P.1.131 Duration of hospitalisation and its modelings

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The authors run a psychiatric unit counting 22 beds for full hospitalisation. In 1989, following the development of systemic and familial theories, the authors considered it expedient to promote hospitalisation in two 9-days periods, interrupted by a return home for 9 days, so as to provide optimum care. According to their hypothesis[1], this way of working makes it possible to prevent the family from reorganising itself without the patient, and on the other hand to include the family from the start in the therapeutic resources. To this end, the direct family is invited to attend a family meeting at the start of the first period. A first biological, psychological and familial correction is carried out during the first stay. After this first phase of bio-psycho-familial engineering, the patient returns home. This makes it possible to evaluate during the second hospitalisation period the impact of the modifications on transactional relations, and to complete and consolidate them. This system, however, is kept flexible in order to avoid uselessly prolonging the slay of patients for whom the full 18 days are not necessary, or, conversely, to extend the period if necessary. Thus, the most pertinent aspect of our system is that it makes maximum use of the family's support, of which it known that it decreases the percentage of relapses[2,3]. Consequently the end of hospitalisation is nol solely determined by improvements in the symptoms, either by themselves or for the patient, but also by the entire "family situation" which must be associated with a level of risk (to the patient of to his family) compatible with a return home in the company of the direct family.

The duration of hospitalisation was compared between a group of 100 patients who were hospitalised before the introduction of this policy and a group of 100 patients hospitalised in 1995 after its introduction. Results revealed that this model had decreased the duration of inpatient stay with mood disorder from 21 to 17 days (Student $p = 0.0492$) and also decreased the average duration of stays at our clinic (16.58) in comparison to the national average inpatient period (17.97 Student $p = 0.053$).

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P.1.132 Meta-analysis of randomized, double-blind, placebo-controlled studies of mirtazapine vs amitriptyline

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Objective: To compare the clinical efficacy and tolerability of mirtazapine with amitriptyline and placebo in the treatment of outpatients with moderate to severe major depressive episode.

Materials and Methods: A total of 580 outpatients of both sexes at least 18 years old, with a DSM III diagnosis of a moderate to severe major depressive episode (296.2 or 296.3), and a total score ≥18 on the first 17 items of the Hamilton Depression Rating Scale-HAMD meeting inclusion and exclusion criteria were randomized to double-blind treatment with either mirtazapine (mirtazapine, n = 194, 5–35 mg/day), amitriptyline (n = 193, 40–280 mg/day) or placebo (n = 193). Efficacy was evaluated weekly by the 17-item HAMD, and the Clinical Global Impression-CGI (Global Improvement). The statistical analysis was performed on an Intent-to-Treat basis (ITT), using analysis of variance (ANOVA) with treatment and investigator as main effects, and the Last Observation Carried Forward Method. The tolerability analysis was performed on all patients who took at least one dose of double-blind medication.

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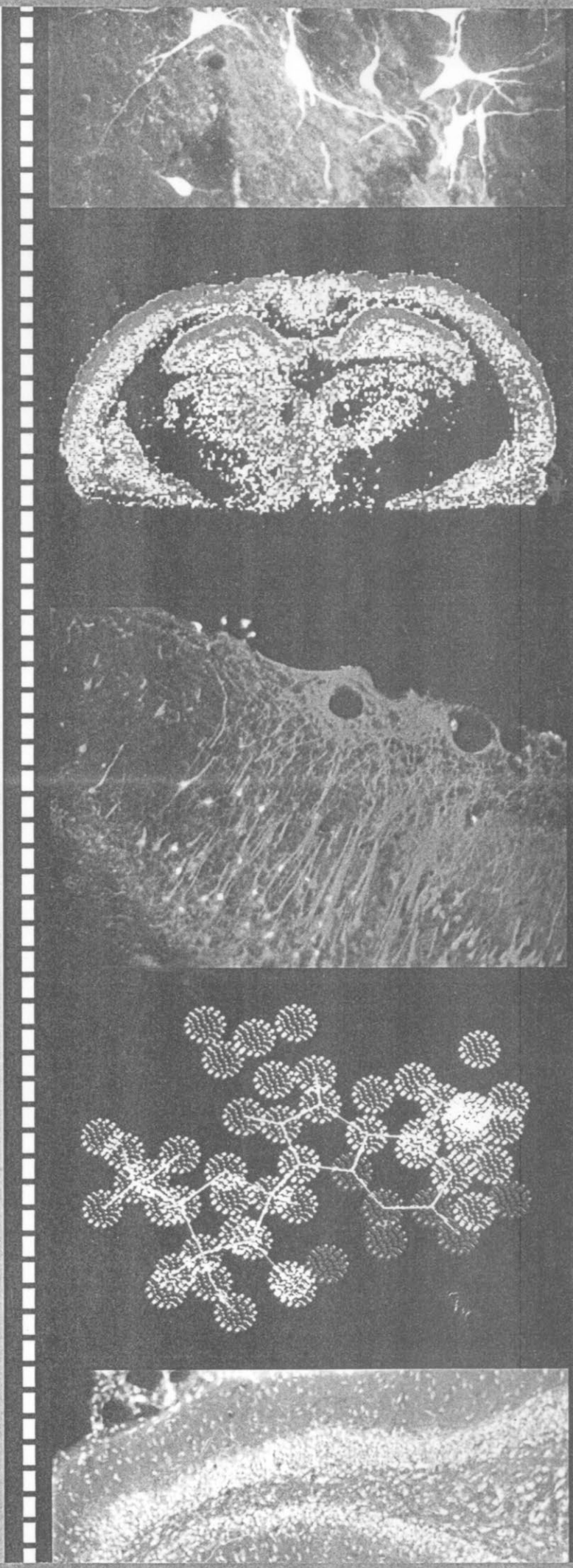

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